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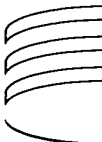
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TAASTRUP 17 April 2001

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USE OF N-SUBSTITUTED AZAHETEROCYCLIC COMPOUNDS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INDICATIONS RELATED TO ANGIOGENESIS

5 FIELD OF INVENTION

The present invention relates to the use of N-substituted azaheterocyclic compounds of the general formulas Ia-Ic for the treatment, prevention, alleviation or amelioration of conditions related to angiogenesis. Hence the compounds can be used in the treatment of patients
10 suffering from a variety of diseases like abnormal tissue growth, neoplasia, hyperplasia, cancer, diabetic retinopathy. The present invention also embraces pharmaceutical compositions comprising those compounds and methods of using the compounds and their pharmaceutical compositions.

15 BACKGROUND OF INVENTION

Tissue growth is critically dependent upon the formation of new capillaries, called angiogenesis or neovascularisation. The process may in pathological conditions be turned on by growth factors, e.g. vascular endothelial growth factor or cytokines, e.g. tumor necrosis factor
20 α . In e.g. cancer, angiogenesis is an important factor for the maintenance and growth of the tumor (Tanaka et al., Cancer Res., 58, 3362-3369, 1998). Angiogenesis is important for neoplastic conditions like cancer as well as diabetic retinopathy. Thus it has been shown that treatments directed against angiogenesis can e.g. inhibit tumor growth (Folkman, J., Breast Cancer Res. and Treat., 36, 190-118, 1995, Tanaka et al., Cancer Res., 58, 3362-
25 3369, 1998).

Thus one object of the invention is to provide compounds which can be used in the treatment of patients suffering from diseases in which neovascularisation or angiogenesis prevails.

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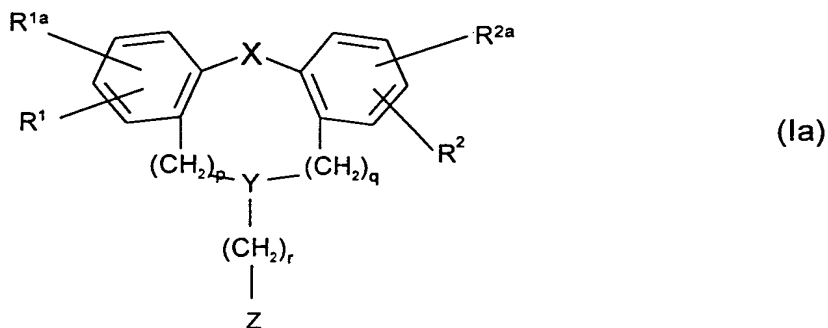
WO 9518793 discloses N-substituted azaheterocyclic carboxylic acids and esters thereof, methods for their preparation, compositions containing them and their use in treatment of hyperalgesic and/or inflammatory conditions.

WO9631497, WO9631498, WO9631499, WO9631481, WO9711071, WO9815548, WO9815546, WO9815550, PCT/DK98/00273, PCT/DK98/00271, DK 0367/98, DK 0366/98, DK 1472/97 and DK 1523/98 discloses N-substituted azaheterocyclic compounds, methods for their preparation, compositions containing them and their use in treatment of hyperalgesic and/or inflammatory conditions as well as as well as their use for treatment of indications caused by or related to the secretion and circulation of insulin antagonising peptides, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.

10 DESCRIPTION OF THE INVENTION

It has surprisingly been found that compounds of the general formulas Ia-Ic below can be used in the treatment, prevention, alleviation or amelioration of an indication related to angiogenesis.

Accordingly, the present invention relates to the use of a compound of the following groups of compounds having the general formula Ia



wherein R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6} -alkyl, C_{1-6} -alkoxy, hydroxy, NR^7R^8 , cyano, methylthio or $-SO_2NR^7R^8$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and

Y is $>\underline{N}-CH_2-$, $>\underline{CH}-CH_2-$ or $>\underline{C}=CH-$ wherein only the underscored atom participates in the ring system; or

Y is $-\underline{\text{C}}\text{H}_2\underline{\text{N}}(-)\text{CH}_2-$, $-\text{CH}_2\underline{\text{N}}(-)\underline{\text{C}}\text{H}_2-$, $-(\underline{\text{C}}=\text{O})\underline{\text{N}}(-)\text{CH}_2-$, $-\text{CH}_2\underline{\text{N}}(-)(\underline{\text{C}}=\text{O})-$, $-\underline{\text{C}}\text{H}_2\underline{\text{C}}\text{H}(-)\text{CH}_2-$, $-\text{CH}_2\underline{\text{C}}\text{H}(-)\underline{\text{C}}\text{H}_2-$, $-\underline{\text{C}}\text{H}_2\underline{\text{C}}(-)=\text{CH}-$, $-\text{CH}=\underline{\text{C}}(-)\underline{\text{C}}\text{H}_2-$, $-\underline{\text{O}}\underline{\text{C}}\text{H}(-)\text{CH}_2-$, $-\text{CH}_2\underline{\text{C}}\text{H}(-)\underline{\text{O}}-$, $-\underline{\text{S}}\underline{\text{C}}\text{H}(-)\text{CH}_2-$, $-\text{CH}_2\underline{\text{C}}\text{H}(-)\underline{\text{S}}-$, wherein only the underscored atom participates in the ring system; or

Y is $-\underline{\text{N}}-$, $-\underline{\text{C}}\text{H}-$, $-\underline{\text{N}}-(\text{C}=\text{O})-$ or $-\underline{\text{C}}=\text{C}(\text{R}^8)-$, wherein only the underscored atom participates in

5 the ring system and R^8 is hydrogen or C_{1-6} -alkyl; or

Y is $-\underline{\text{C}}\text{H}-\text{O}-$ or $-\underline{\text{C}}\text{H}-\text{S}(\text{O})_y$, wherein y is 0, 1 or 2, or $-\text{N}(\text{R}^8)-$ wherein R^8 is hydrogen or C_{1-6} -alkyl, and wherein only the underscored atom participates in the ring system; and

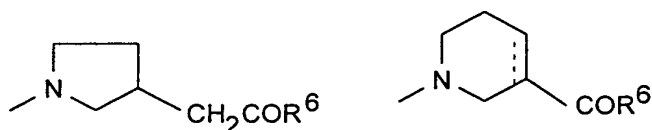
X is completion of an optional bond, ortho-phenylene, $-\text{O}-$, $-\text{S}-$, $-\text{C}(\text{R}^7\text{R}^8)-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$,
 10 CH_2- , $-\text{CH}_2-\text{CH}=\text{CH}-$, $-\text{CH}_2-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{N}(\text{R}^8)-(\text{C}=\text{O})-$, $-(\text{C}=\text{O})-\text{N}(\text{R}^8)-$, $-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-$, $-\text{OCH}_2\text{O}-$, $-\text{CH}_2\text{OCH}_2-$, $-\text{S}-\text{CH}_2-$, $-\text{CH}_2-\text{S}-$, $-(\text{CH}_2)\text{N}(\text{R}^8)-$, $-\text{N}(\text{R}^8)(\text{CH}_2)-$, $-\text{N}(\text{CH}_3)\text{SO}_2-$, $-\text{SO}_2\text{N}(\text{CH}_3)-$, $-\text{CH}(\text{R}^9)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{R}^9)-$, $-(\text{C}=\text{O})-$, $-\text{N}(\text{R}^8)-$ or $-(\text{S}=\text{O})-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

15

p and q independently are 0 or 1; and

r is 0, 1, 2, 3 or 4; and

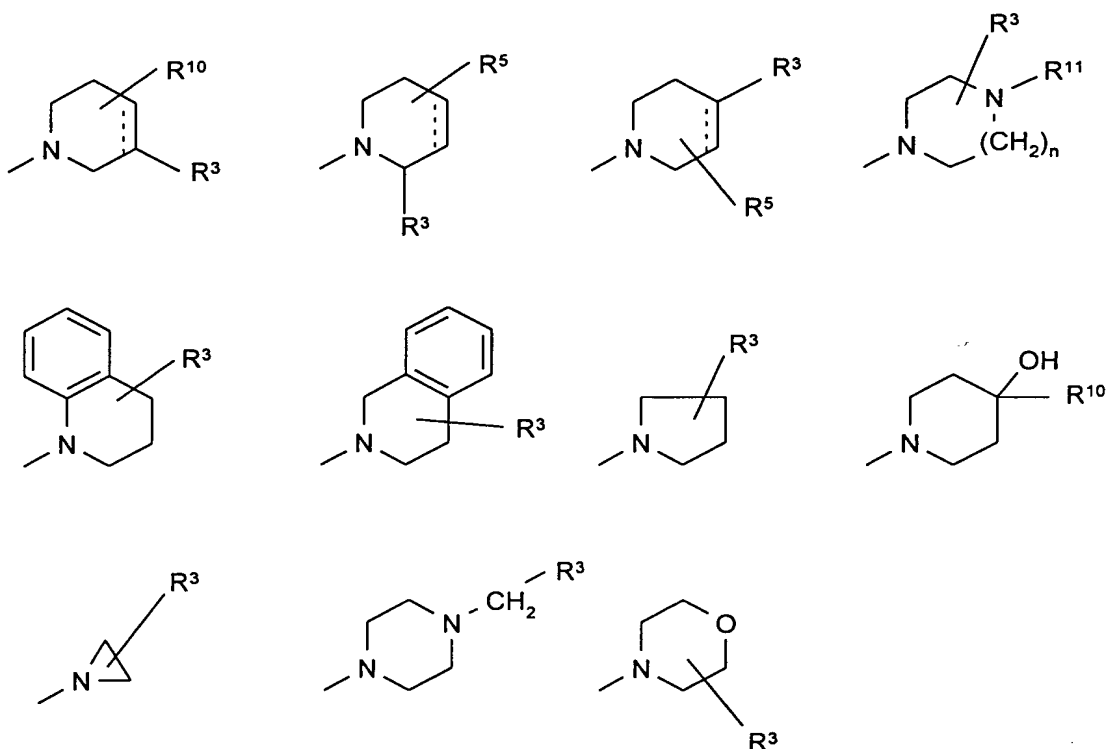
20 Z is selected from



wherein R^6 is OH or C_{1-6} -alkoxy; and

.... is optionally a single bond or a double bond; or

25 Z is selected from



wherein n is 1 or 2;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

5 R^4 is $-OH$, $-NH_2$, $-NHOH$ or C_{1-6} -alkoxy; and

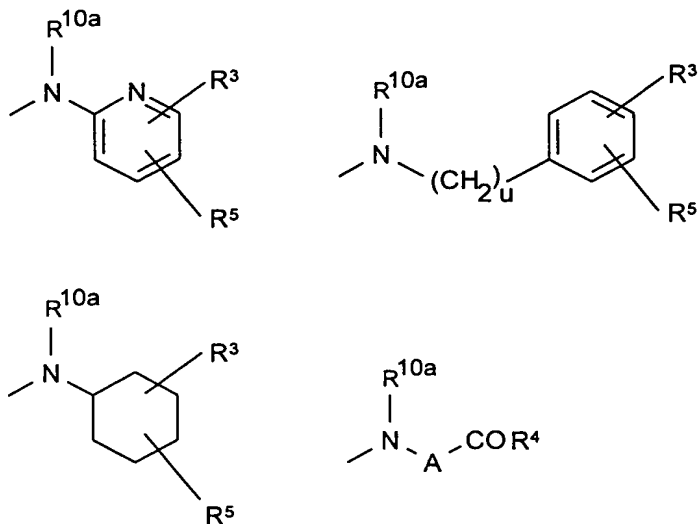
R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{10} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{11} is hydrogen or C_{1-6} -alkyl; and

10 --- is optionally a single bond or a double bond; or

11 Z is selected from



wherein u is 0 or 1;

R^3 is $-(\text{CH}_2)_m\text{OH}$ or $-(\text{CH}_2)_s\text{COR}^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

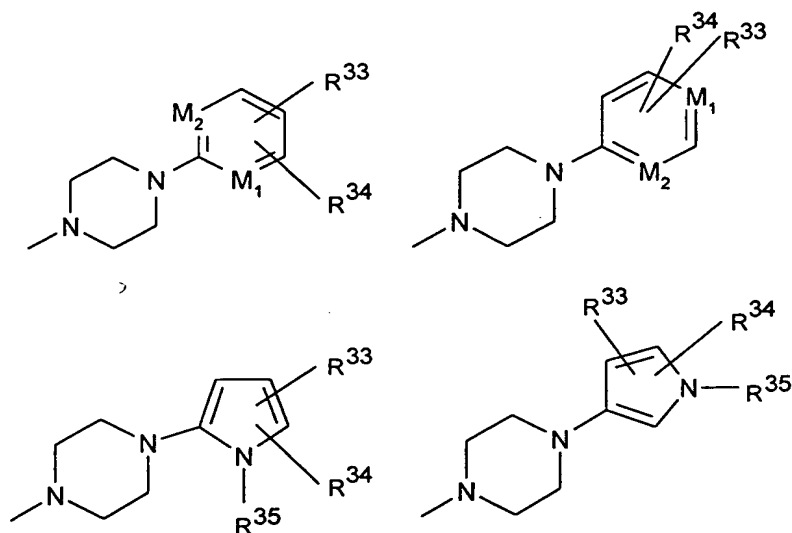
5 R^4 is $-\text{OH}$, $-\text{NH}_2$, $-\text{NHOH}$ or C_{1-6} -alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{10a} is hydrogen or C_{1-6} -alkyl; and

A is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; or

10 Z is selected from



wherein M_1 and M_2 independently are C or N; and

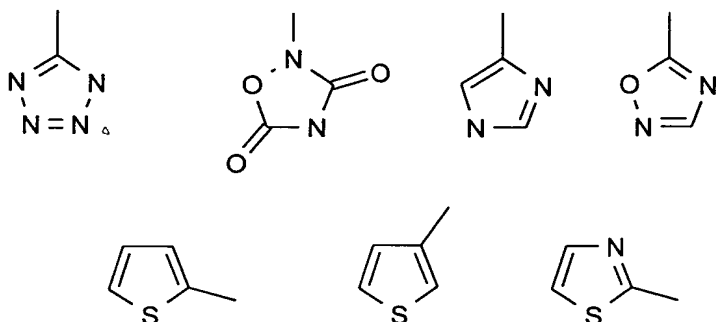
R^{35} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6} -alkoxy or NHR^{32} , wherein R^{32} is hydrogen or C_{1-6} -

5 alkyl, and w is 0, 1 or 2; or

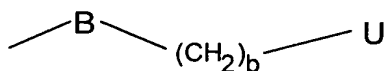
R^{34} is selected from



or

10

Z is

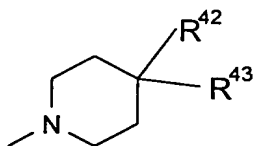


wherein b is 0, 1, 2, 3 or 4; and

15 B is $-CH=CR^{49}-$, $-CR^{49}=CH-$, $-C\equiv C-$, $-(C=O)-$, $-(C=CH_2)-$, $-(CR^{49}R^{40})-$, $-CH(OR^{41})-$, $-CH(NHR^{41})-$, phenylene, C_{3-7} -cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C_{1-6} -unbranched alkyl, C_{3-6} -branched alkyl or C_{3-7} -cycloalkyl and wherein R^{41} is hydrogen or C_{1-6} -alkyl; and

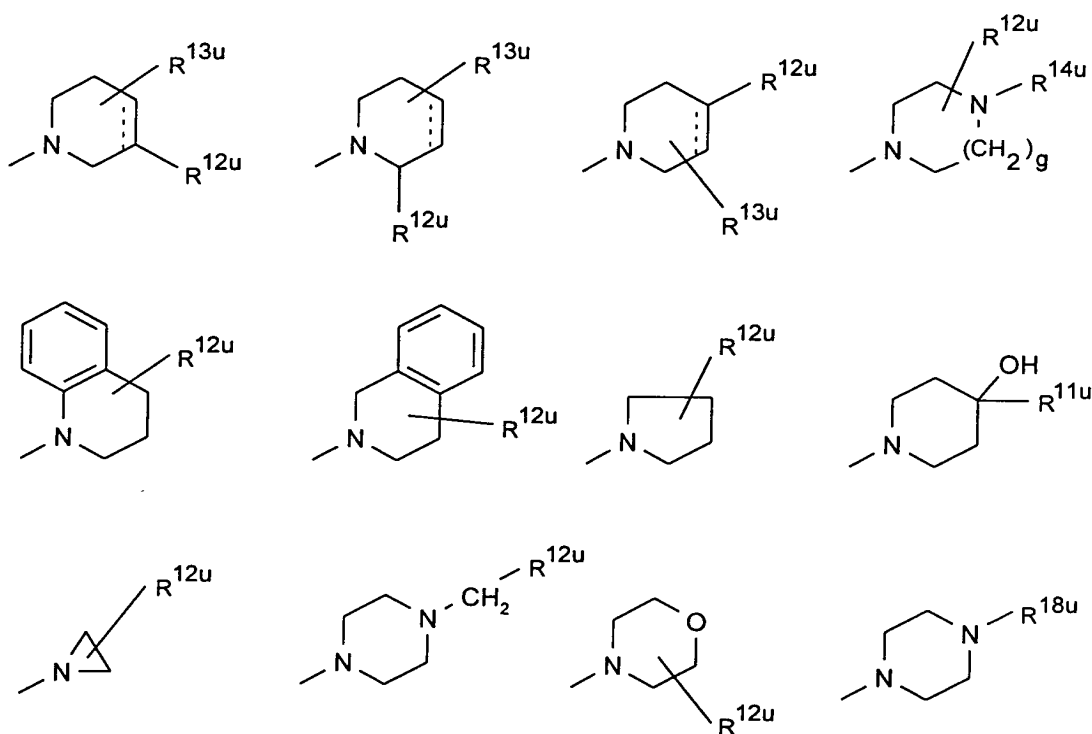
U is

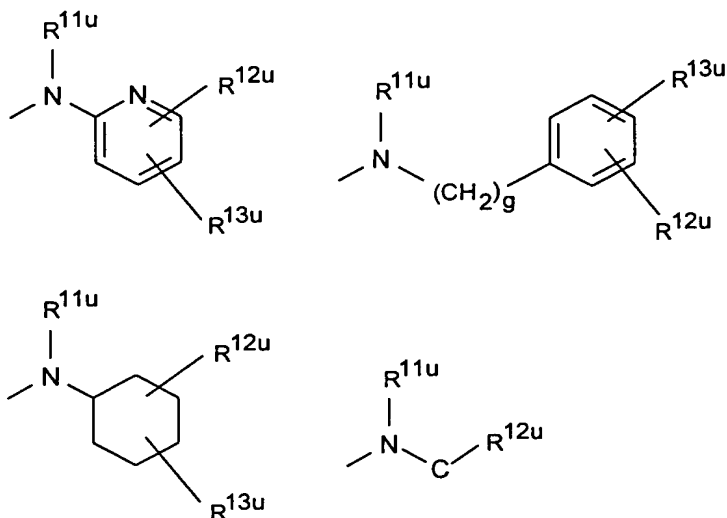
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wherein R^{42} is hydrogen, $-(CH_2)_cOH$ or $-(CH_2)_dCOR^{47}$ wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R^{47} is $-OH$, $-NHR^{44}$ or C_{1-6} -alkoxy wherein R^{44} is hydrogen or C_{1-6} -alkyl; and

- 5 R^{43} is cyano, $-NR^{45}R^{46}$, $-NR^{45}-V$ or $-(CHR^{48})_e-V$ wherein R^{45} and R^{46} independently are hydrogen or C_{1-6} -alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R^{48} is hydrogen, halogen, cyano, trifluoromethyl, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-NR^{45}R^{46}$ or $-COOH$, and wherein V is C_{3-8} -cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C_{1-6} -alkyl or C_{1-6} -alkoxy; or U is selected from





wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen,

5 trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is $-OH$, $-NHR^{20u}$ or C_{1-6} -alkoxy wherein R^{20u} is hydrogen or C_{1-6} -alkyl; and

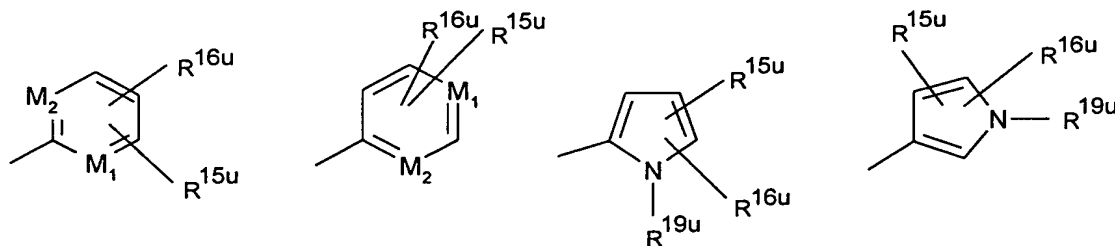
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{14u} is hydrogen or C_{1-6} -alkyl; and

10 C is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; and

... is optionally a single bond or a double bond; and

R^{18u} is selected from



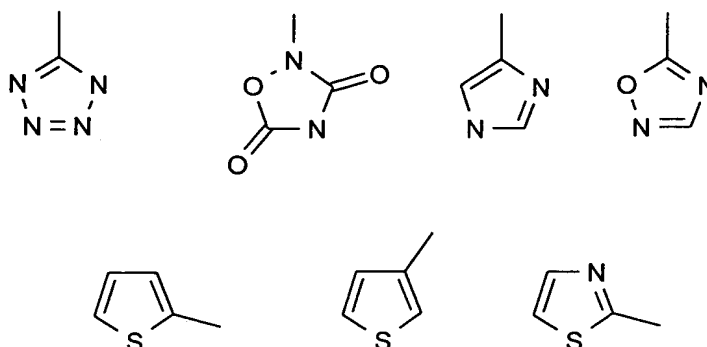
wherein M_1 and M_2 independently are C or N; and

15 R^{19u} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

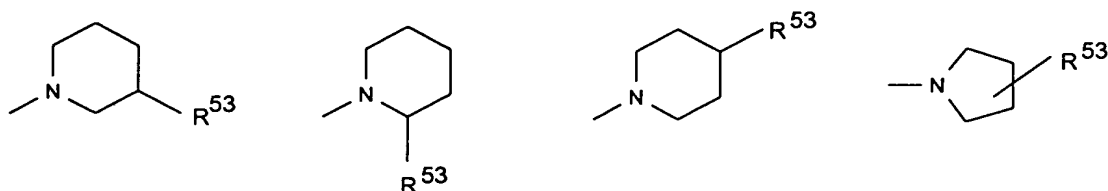
R^{16u} is selected from



or

5

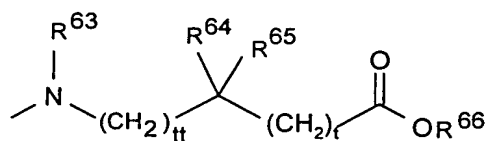
Z is selected from



wherein R^{53} is $-(CH_2)_{pp}COOH$ wherein pp is 2, 3, 4, 5 or 6; or

10

Z is



wherein tt and t independently are 0, 1 or 2; and

15

R^{63} is H, C_{1-6} -alkyl or optionally substituted benzyl;

R^{64} and R^{65} independently are H, C_{1-8} -alkyl, C_{3-7} -cycloalkyl, phenyl, thienyl, benzyl, or R^{64} and

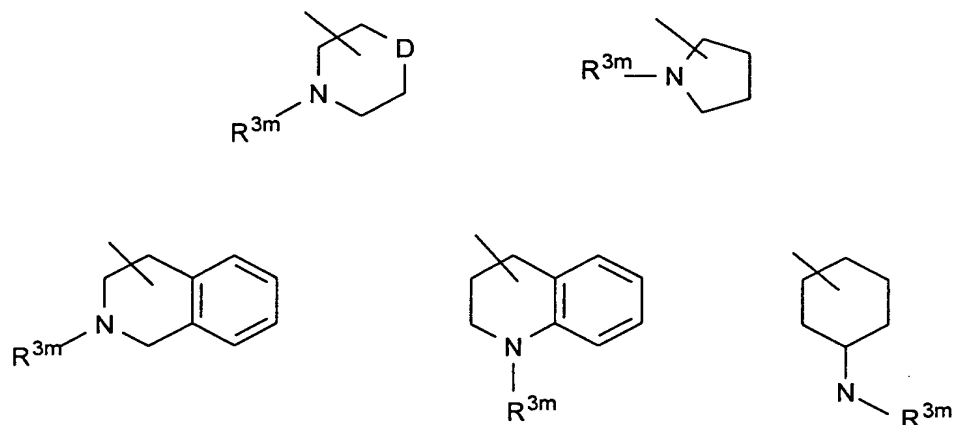
R^{65} together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring;

and

R^{66} is H or C_{1-6} -alkyl; or

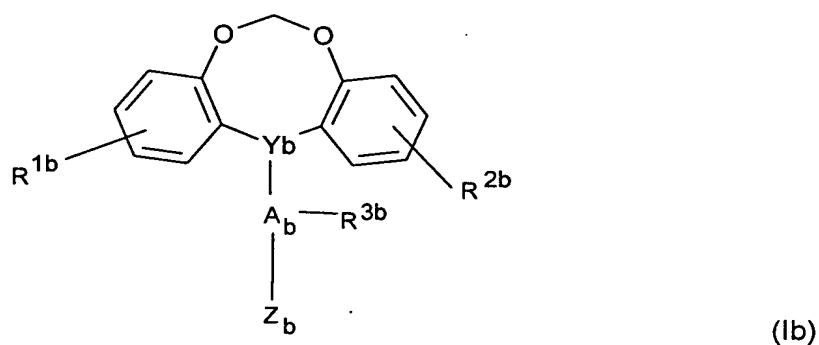
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Z is selected from

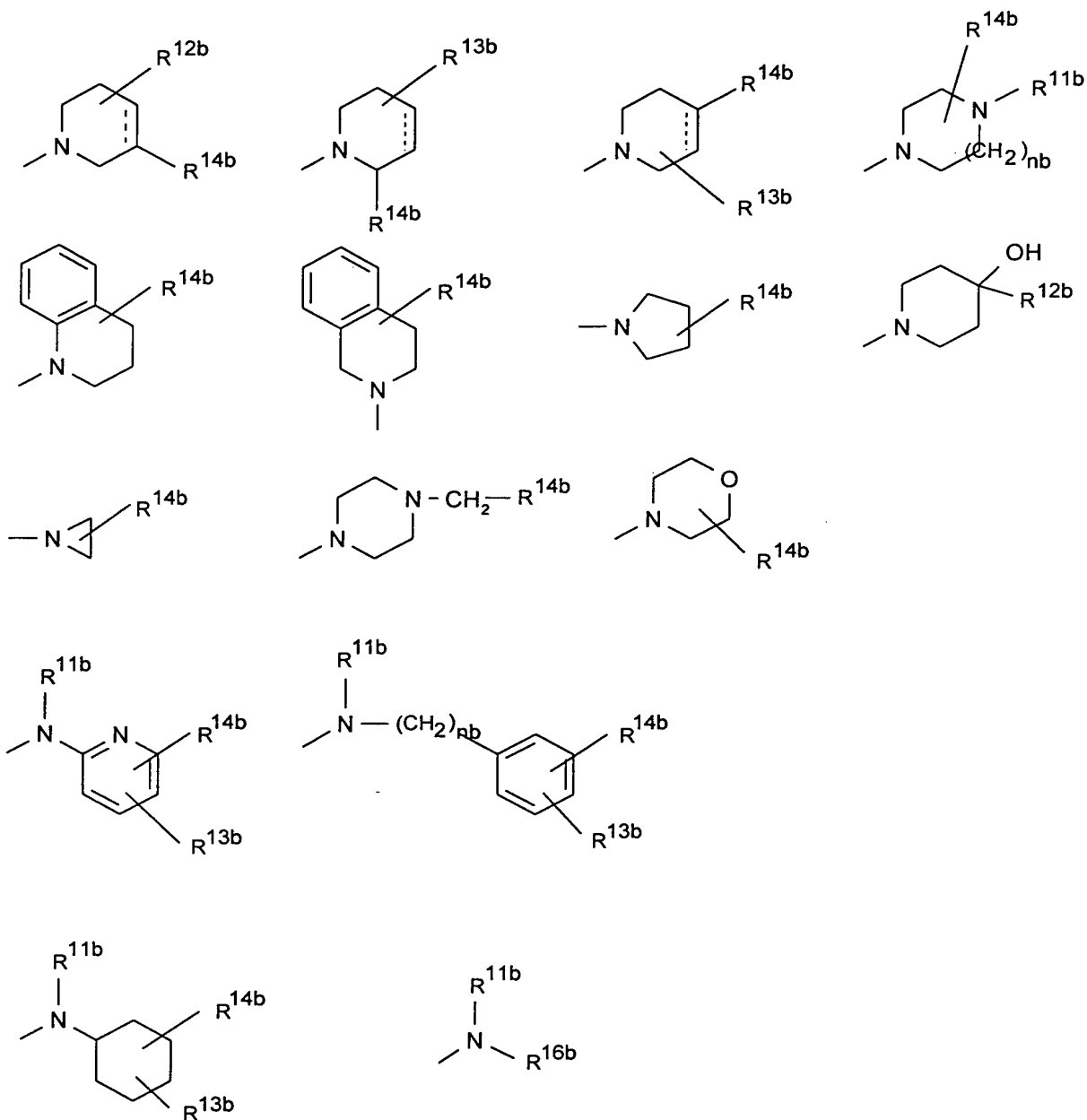


wherein D is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$ or $-\text{N}(\text{R}^7)-$ wherein R^7 is hydrogen or C_{1-6} -alkyl; and
 R^{3m} is $-(\text{CH}_2)_{mm}\text{OH}$ or $-(\text{CH}_2)_{mp}\text{COR}^4$ wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH_2 ,
 5 NHOH or C_{1-6} -alkoxy; or

having the general formula Ib



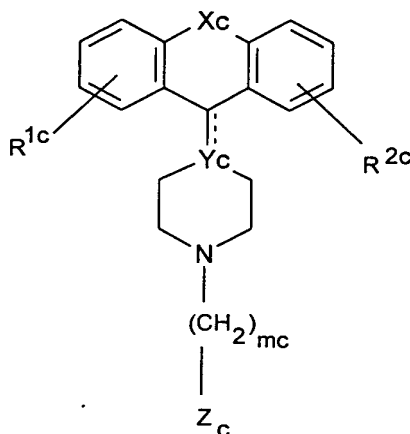
wherein R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy,
 C_{1-6} -alkyl or C_{1-6} -alkoxy; and
 R^{3b} is hydrogen or C_{1-3} -alkyl; and
 A_b is C_{1-3} -alkylene; and
 15 Y_b is $>\underline{\text{C}}\text{H}-\text{CH}_2-$, $>\underline{\text{C}}=\text{CH}-$, $>\underline{\text{C}}\text{H}-\text{O}-$, $>\underline{\text{C}}=\text{N}-$, $>\underline{\text{N}}-\text{CH}_2-$ wherein only the underscored atom
 participates in the ring system; and
 Z_b is selected from



- 5 wherein nb is 1 or 2; and
 R^{11b} is hydrogen or C₁₋₆-alkyl; and
 R^{12b} is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and
 R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and
 10 R^{14b} is -(CH₂)_{mb}OH or -(CH₂)_{tb}COR^{15b} wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and
 wherein R^{15b} is -OH, NH₂, -NHOH or C₁₋₆-alkoxy; and

R^{16b} is C_{1-6} -alkyl or $-B_b-COR^{15b}$, wherein B_b is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene and R^{15b} is the same as above; and
 ... is optionally a single bond or a double bond; or

5 having the general formula 1c



(1c)

wherein R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or
 10 C_{1-6} -alkoxy;

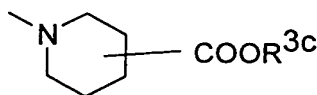
X_c is ortho-phenylene, -O-, -S-, $-C(R^{6c}R^{7c})-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-$
 $(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^{8c})-(C=O)-$, $-(C=O)-N(R^{8c})-$, $-O-CH_2-$, $-CH_2-$
 $O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^{8c})-$, $-N(R^{8c})(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$,
 15 $-CH(R^{10c})CH_2-$, $-CH_2CH(R^{10c})-$, $-(C=O)-$, $-N(R^{9c})-$ or $-(S=O)-$ wherein R^{6c} , R^{7c} , R^{8c} and R^{9c} inde-

Y_c is C or N;

... is optionally a single bond or a double bond, and ... is a single bond when Y_c is N;

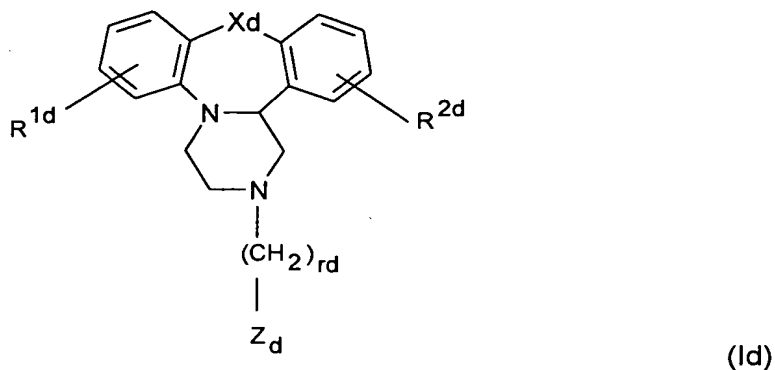
mc is 1, 2, 3, 4, 5 or 6; and

Z_c is $-COOR^{3c}$ or



wherein R^{3c} is H or C_{1-6} -alkyl; or

having the general formula Id



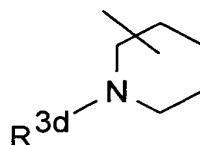
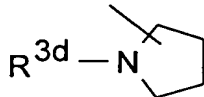
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wherein R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

X_d is -O-, -S- or -S(=O)-; and

rd is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10; and

10 Z_d is selected from



wherein R^{3d} is $-(CH_2)_{md}OH$ or $-(CH_2)_{pd}COR^{4d}$ wherein md and pd independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2 , $NHOH$ or C_{1-6} -alkoxy; or

a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention, alleviation or amelioration of an indication related to angiogenesis.

15

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The compounds according to the invention may exist as geometric and optical isomers and all isomers, as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallisation of suitable salts.

Preferably, the compounds according to the invention exist as the individual geometric or optical isomers.

The compounds according to the invention may optionally exist as pharmaceutically acceptable acid addition salts, metal salts or, optionally alkylated, ammonium salts.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also included are the hydrates of the above mentioned acid addition salts which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or by precipitation or crystallisation.

The compounds according to the invention may be administered in a pharmaceutically acceptable acid addition salt form or where possible as a metal or a lower alkylammonium salt. Such salt forms exhibit approximately the same order of activity as the free base forms.

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The terms "C₁₋₆-alkyl" and "C₁₋₈-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 and 1 to 8 carbon atoms respectively. Examples of such groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, iso-hexyl, 4-methylpentyl, neopentyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "C₁₋₆-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₆-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The terms "C₃₋₇-cycloalkyl" and "C₃₋₈-cycloalkyl" as used herein, represents a carbocyclic group having from 3 to 7 carbon atoms and having from 3 to 8 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

The term "C₃₋₇-cycloalkylene" as used herein represents a bisubstituted carbocyclic group having from 3 to 7 carbon atoms e.g. cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene and the like.

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, naphthyl (1-naphthyl or 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), phenanthrenyl, fluorenyl, indenyl and the like.

The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, pyranlyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, quinoxolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl and the like. Heteroaryl is also intended to include the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially or fully hydrogenated derivatives are pyrrolinyl, pyrazolinyl, indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, diazepinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, oxazolinyl, oxazepinyl, aziridinyl and tetrahydrofuranlyl.

The term "3- to 8-membered carbocyclic ring" as used herein refers to a monocyclic unsaturated or saturated ring containing from 3 to 8 carbon atoms. The term includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

In a preferred embodiment of the invention in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

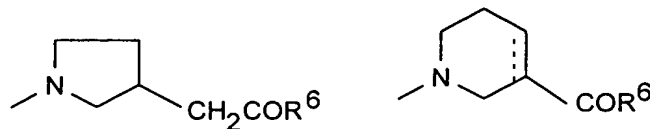
Y is $>\underline{N}-CH_2-$, $>\underline{CH}-CH_2-$ or $>\underline{C}=CH-$ wherein only the underscored atom participates in the ring system; and

X is $-O-$, $-S-$, $-C(R^7R^8)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-O-CH_2-$, $-(C=O)-$ or $-(S=O)-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and

p and q are 0, and

r is 1, 2 or 3; and

Z is selected from



wherein R^6 is OH or C_{1-6} -alkoxy; and

... is optionally a single bond or a double bond; or a pharmaceutically acceptable salt thereof.

Preferred compounds of the present invention include

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

5 (R)-1-(3-(Fluoren-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(Thioxanthen-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

10

(R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-butyl)-3-piperidinecarboxylic acid;

15 (R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

20 (R)-1-(3-(10H-Phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

25

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-pyrrolidinacetic acid;

(R)-1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

30

(R)-1-(3-(2-Trifluoromethyl-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Oxo-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-10-Oxa-5-aza-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

- 5 1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

(R)-1-(3-(6,7-Dihydro-5H-dibenzo[b,g]azocin-12-yl)-1-propyl)-3-piperidinecarboxylic acid;

- 10 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

15

(R)-1-(3-(10-Methyl-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9(H)-Oxo-10H-acridin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

20

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(2-(6,11-Dihydrodibenz[b,e]oxepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

25

(R)-1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

- 30 (R)-1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

- 5 (Z)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(E)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

10

(R)-1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride.

In another preferred embodiment of the invention in formula Ia

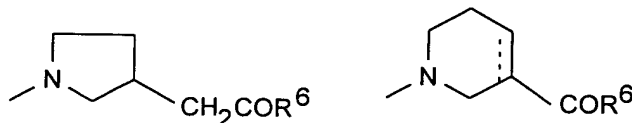
- 15 R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

Y is $\underline{C}H_2N(-)CH_2-$, $-CH_2N(-)\underline{C}H_2-$, $-(\underline{C}=O)N(-)CH_2-$, $-CH_2N(-)(\underline{C}=O)-$, $\underline{C}H_2CH(-)CH_2-$, $-CH_2CH(-)\underline{C}H_2-$, $\underline{C}H_2C(-)=CH-$, $-CH=\underline{C}(-)\underline{C}H_2-$, $\underline{O}CH(-)CH_2-$, $-CH_2CH(-)\underline{O}-$, $\underline{S}CH(-)CH_2-$, $-CH_2CH(-)\underline{S}-$, wherein only the underscored atom participates in the ring system; and

- 20 X is $-O-$, $-S-$, $-C(R^7R^8)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$, $-CH_2-S-$, $-N(R^8)-$, $-(C=O)-$ or $-(S=O)-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and
p and q independently are 0 or 1; and

r is 1, 2 or 3; and

- 25 Z is selected from



wherein R^6 is OH or C_{1-6} -alkoxy; and

... is optionally a single bond or a double bond; or
a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

5 (R)-1-(3-(6,11-Dioxo-6,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6,11-Dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

10 (R)-1-(3-(5,11-Dihydro-10H-dibenzo[b,e][1,4]diazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenzo[b,f][1,4]thiazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

15 (R)-1-(3-(11H-Dibenz[b,f][1,4]oxazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenz[b,f][1,4]oxathiepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenzo[b,e][1,4]dithiepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

20 (R)-1-(3-(11H-Dibenz[b,e][1,4]oxathiepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-10H-dibenz[b,g][1,5]oxazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

25 (R)-1-(3-(11,12-Dihydro-10H-dibenzo[b,g][1,5]thiazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(11,12-Dihydro-6H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

30 1-(3-(11,12-Dihydro-5H-dibenzo[a,e]cycloocten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Oxo-11,12-dihydro-5H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(7,12-Dihydro-6H-dibenzo[a,d]cycloocten-6-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

- 5 1-(3-(5-Methyl-5,11-dihydro-dibenz[b,f]azepin-10-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Oxo-5,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

- 10 (R)-1-(3-(11-Oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6-Oxo-11,12-dihydro-5H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

15

(R)-1-(3-(10,11-Dihydro-dibenz[b,f][1,4]oxazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5,6,11,12-Tetrahydro-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

- 20 (R)-1-(3-(11-Oxo-6,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Methyl-dibenz[b,f]azepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

- 25 (R)-1-(3-(6,7-Dihydro-5H-dibenz[b,g][1,5]oxazocin-6-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-dibenz[a,e]cycloocten-5-yl)-1-propyl)-3-piperidinecarboxylic acid.

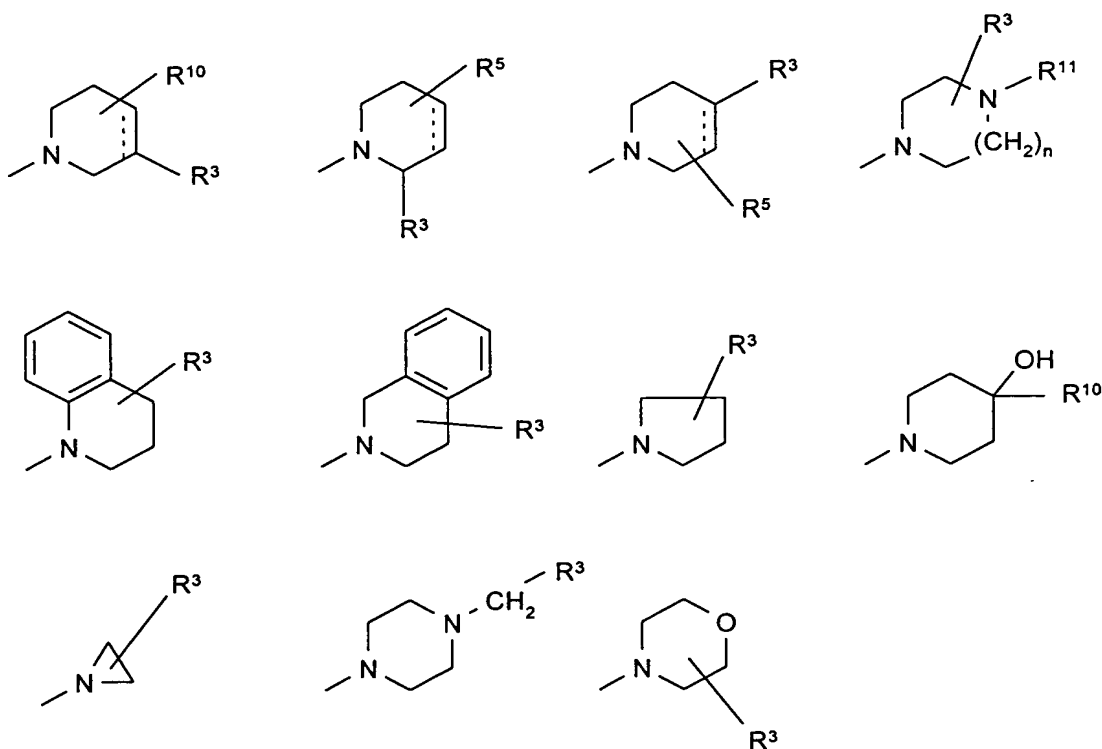
In another preferred embodiment of the invention in formula Ia

- 30 R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, NR⁷R⁸, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and Y is >N-CH₂- , >CH-CH₂- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -S-CH₂-, -CH₂-S-, -N(R⁸)-, -(C=O)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and p and q are 0; and

5 r is 1, 2 or 3; and

Z is selected from



wherein n is 1 or 2; and

10 R³ is -(CH₂)_mOH or -(CH₂)_sCOR⁴ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein R⁴ is -OH, -NH₂, -NHOH or C₁₋₆-alkoxy; and

R⁵ is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

R¹⁰ is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

15 R¹¹ is hydrogen or C₁₋₆-alkyl; and

... is optionally a single bond or a double bond; or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

- 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidine-carboxamide;
- 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;
- 5 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperidinecarboxylic acid;
- (1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidiny)methanol;
- 10 4-(4-Chlorophenyl)-1-(3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinol;
- 4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperazinecarboxylic acid;
- (2S,4R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-hydroxy-2-
- 15 pyrrolidinecarboxylic acid;
- 4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-morpholinecarboxylic acid;
- 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-aziridinecarboxylic acid;
- 20 2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1,2,3,4-tetrahydro-4-isoquinolinecarboxylic acid;
- 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-methyl-[1,4]-diazepane-6-
- 25 carboxylic acid;
- 2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid;
- 30 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid hydroxamide;
- (4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)piperazin-1-yl)acetic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperazinecarboxylic acid;

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1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidineacetic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

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(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxamide;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-pyrrolidinecarboxylic acid;

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(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-pyrrolidinecarboxylic acid;

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1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-4-piperidinecarboxylic acid;

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1-(3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidineacetic acid;

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1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-methyl-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-quinuclidiniumcarboxylate;

1-(3-(2,8-Dibromo-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

5 1-(3-(3,7-Dichloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

10

1-(3-(3,7-Dimethyl-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

15

1-(3-(3-Dimethylamino-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

20

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

25

1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Chloro-6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

30

1-(2-(2-Chloro-6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

- 5 1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

- 10 1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-2-piperidineacetic acid;

- 15 1-(3-(Phenothiazin-10-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-2-piperidinecarboxylic acid;

- 20 1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]oxepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid.

- 25 In another preferred embodiment of the invention in formula Ia

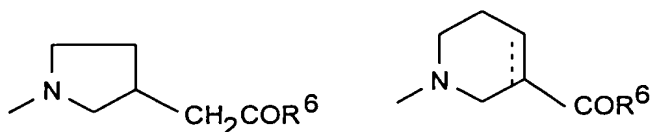
R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

Y is $\text{>}\underline{\text{N}}\text{-CH}_2\text{-}$, $\text{>}\underline{\text{C}}\text{H-CH}_2\text{-}$ or $\text{>}\underline{\text{C}}\text{=CH-}$ wherein only the underscored atom participates in the ring system; and

- 30 X is ortho-phenylene, $\text{-CH}_2\text{-(C=O)-}$, $\text{-(C=O)-CH}_2\text{-}$, $\text{-S-CH}_2\text{-}$, $\text{-CH}_2\text{-S-}$, $\text{-(CH}_2\text{)N(R}^8\text{)-}$, $\text{-N(R}^8\text{)(CH}_2\text{)-}$, $\text{-N(CH}_3\text{)SO}_2\text{-}$, $\text{-SO}_2\text{N(CH}_3\text{)-}$, $\text{-CH(R}^9\text{)CH}_2\text{-}$ or $\text{-CH}_2\text{CH(R}^9\text{)-}$ wherein R⁸ is hydrogen or C₁₋₆-alkyl and R⁹ is C₁₋₆-alkyl or phenyl; and
p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



- 5 wherein R⁶ is OH or C₁₋₆-alkoxy; and
 is optionally a single bond or a double bond; or
 a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

10

1-(3-(9H-Tribenz[b,d,f]azepin-9-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(Tribenzo[a,c,e]cyclohepten-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

15

1-(3-(5-Methyl-5,6-dihydrodibenz[b,e]azepin-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Methyl-6H-dibenzo[c,f][1,2]thiazepin-5,5-dioxide-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

20

1-(3-(10-Methyl-10,11-dihydro-5H-dibenzo[b,e]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10-Phenyl-10,11-dihydro-5H-dibenzo[b,e]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

25

1-(3-(6,11-Dihydro-11H-dibenzo[b,e][1,4]thiazepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10-Methyl-10,11-dihydro-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

30

(R)-1-(3-(10-Oxo-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

- 5 (R)-1-(3-(6-Methyl-6,11-dihydro-dibenzo[c,f][1,2,5]thiadiazepin-5,5-dioxide-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Methyl-5,6-dihydrodibenz[b,e]azepin-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

10

(R)-1-(3-(9H-Tribenzo[a,c,e]cyclohepten-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9H-Tribenzo[b,d,f]azepine-9-yl)propyl)-3-piperidinecarboxylic acid.

- 15 In another preferred embodiment of the invention in formula Ia

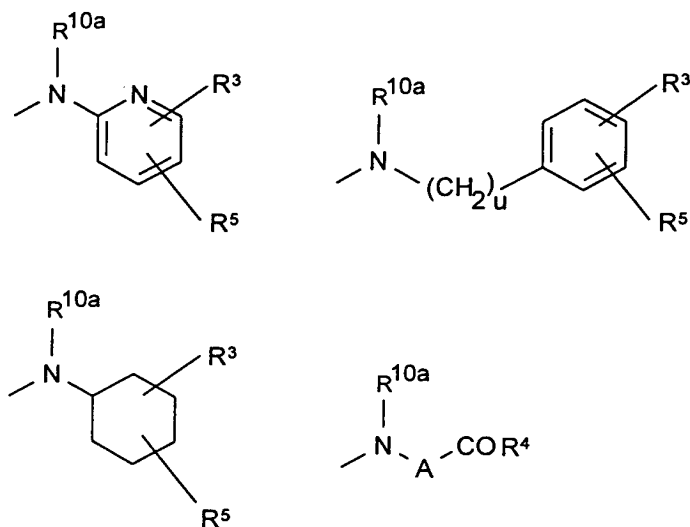
R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

Y is $>\underline{N}-CH_2-$, $>\underline{CH}-CH_2-$ or $>\underline{C}=CH-$ wherein only the underscored atom participates in the ring system; and

- 20 X is $-O-$, $-S-$, $-C(R^7R^8)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$, $-CH_2-S-$, $-N(R^8)-$, $-(C=O)-$ or $-(S=O)-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and
p and q are 0; and

r is 1, 2 or 3; and

- 25 Z is selected from



wherein u is 0 or 1;

R³ is -(CH₂)_mOH or -(CH₂)_sCOR⁴ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

5 R⁴ is -OH, -NH₂, -NHOH or C₁₋₆-alkoxy; and

R⁵ is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

R^{10a} is hydrogen or C₁₋₆-alkyl; and

A is C₁₋₆-alkylene, C₂₋₆-alkenylene or C₂₋₆-alkynylene; or

a pharmaceutically acceptable salt thereof.

10

Further preferred compounds of the invention include:

3-(N-Methyl-N-(3-(10,11-dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)propionic acid;

15

4-(N-Methyl-N-(3-(10,11-dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)butyric acid;

3-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)propionic acid;

20

2-(N(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methyl-amino)succinic acid;

2-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

2-(N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)nicotinic acid;

2-((N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)methyl)benzoic
5 acid;

2-((N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)-1-cyclohexanecarboxylic acid;

10 2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propylamino)pyridin-3-ol;

3-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

2-((3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)benzoic acid;

15

2-(N-(3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

5-Bromo-2-(N-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)benzoic acid.

20

In another preferred embodiment of the invention in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy;

Y is $>\underline{N}$ -CH₂-, $>\underline{CH}$ -CH₂-, $>\underline{C}$ =CH- or $>\underline{CH}$ -O- wherein only the underscored atom partici-
25 pates in the ring system; and

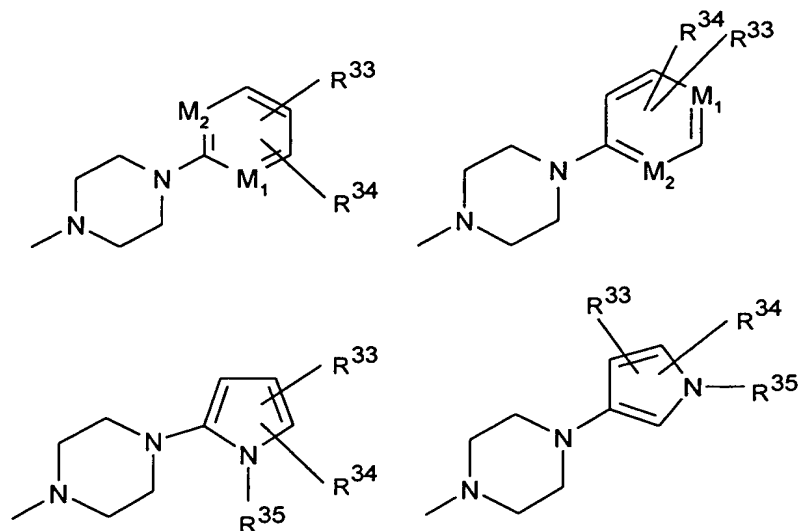
X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R^8)-, -N(R^8)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R^9)CH₂-, -CH₂CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are

30 hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



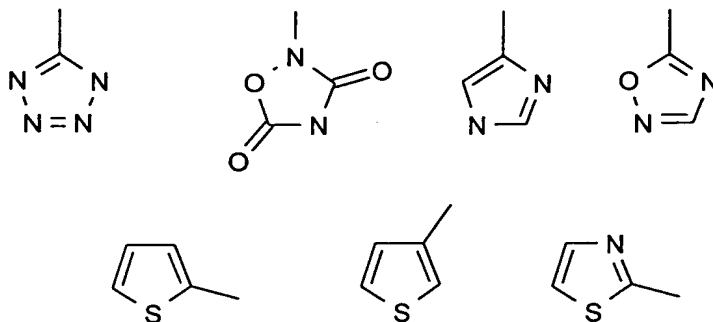
wherein M_1 and M_2 independently are C or N; and

R^{35} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

5 R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6} -alkoxy or NHR^{32} , wherein R^{32} is hydrogen or C_{1-6} -alkyl, and w is 0, 1 or 2; or

R^{34} is selected from



10

or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

15

2-(4-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(2,10-Dichloro-12H-dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-piperazin-1-yl)-3-pyridinecarboxylic acid;

- 5 2-(4-(3-(12H-Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(2-Chloro-12H-dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-piperazin-1-yl)-3-pyridinecarboxylic acid;

10

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(2-pyridyl)piperazine;

15

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propyl)-1-piperaziny)-3-pyridine-carboxylic acid;

2-(4-(2-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-ethyl)-1-piperaziny)-3-pyridinecarboxylic acid;

20

6-(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1-piperaziny)-2-pyridinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1-piperaziny)-3-pyridinecarboxylic acid;

25

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperaziny)-5-pyridinecarboxylic acid;

30

2-(4-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperaziny)-3-pyridinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(2-nitrophenyl)-piperazine;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1-piperazinyl)-benzonitrile;

5 2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1-piperazinyl)-benzoic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(3-trifluoromethyl-2-pyridyl)piperazine;

10

2-(4-(2-(6,11-Dihydro-dibenzo[b,e]thiepin-11-ylidene)ethyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

15

2-(4-(3-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

2-(4-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)ethyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

20

6-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperazin-1-yl)-2-pyridinecarboxylic acid;

2-(4-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

25

6-(4-(3-(Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-piperazin-1-yl)-pyridine-2-carboxylic acid.

In another preferred embodiment of the invention in formula Ia

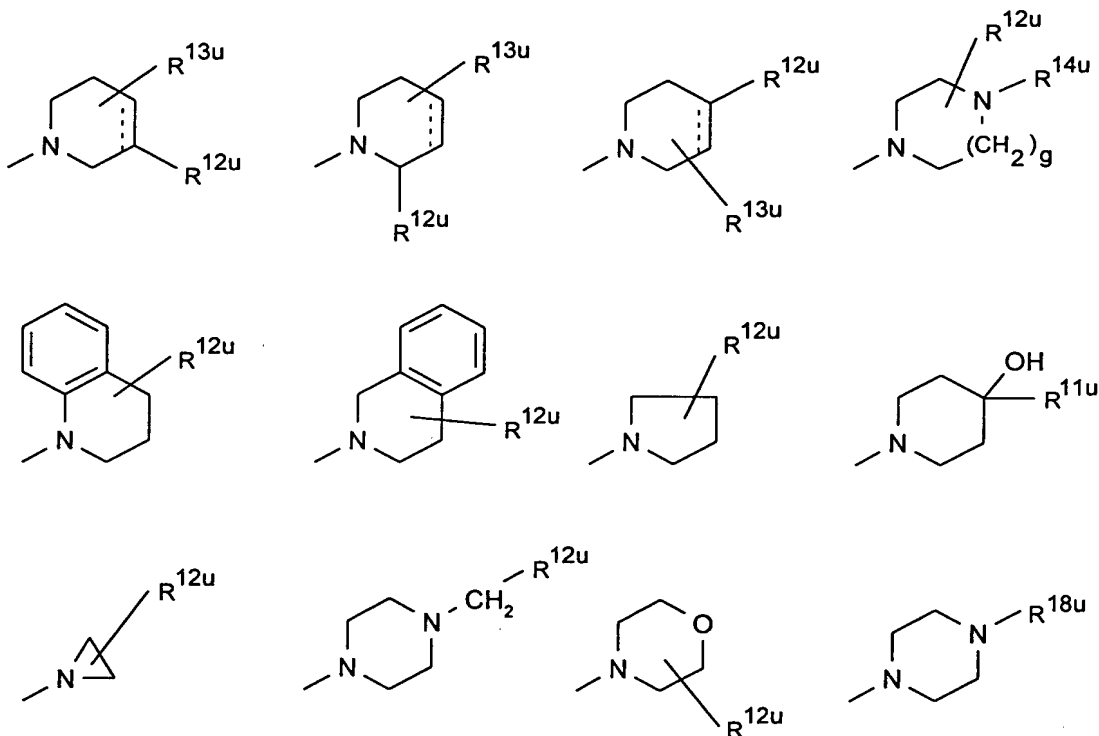
30 R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

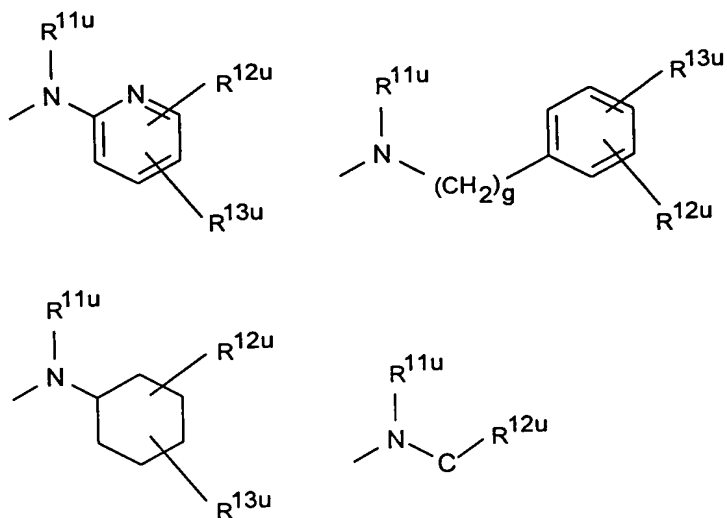
Y is >N-, >CH-, >N-(C=O)- or >C=C(R⁸)-, wherein only the underscored atom participates in the ring system and R⁸ is hydrogen or C₁₋₆-alkyl; and

- X is ortho-phenylene, -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -CH₂OCH₂-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R⁹)CH₂-, -CH₂CH(R⁹)-, -(C=O)-, -N(R⁸)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and wherein R⁹ is C₁₋₆-alkyl or phenyl;
- 5 and p and q are 0; and
r is 0, 1, 2, 3 or 4; and
Z is



- wherein b is 0, 1, 2, 3 or 4; and
B is -CH=CR⁴⁹-, -CR⁴⁹=CH-, -C≡C-, -(C=O)-, -(C=CH₂)-, -(CR⁴⁹R⁴⁰)-, -CH(OR⁴¹)-, -CH(NHR⁴¹)-, phenylene, C₃₋₇-cycloalkylene or the completion of a bond, wherein R⁴⁹ and R⁴⁰
- 15 independently are hydrogen, C₁₋₆-unbranched alkyl, C₃₋₆-branched alkyl or C₃₋₇-cycloalkyl and wherein R⁴¹ is hydrogen or C₁₋₆-alkyl; and
U is selected from





wherein g is 0, 1 or 2; and

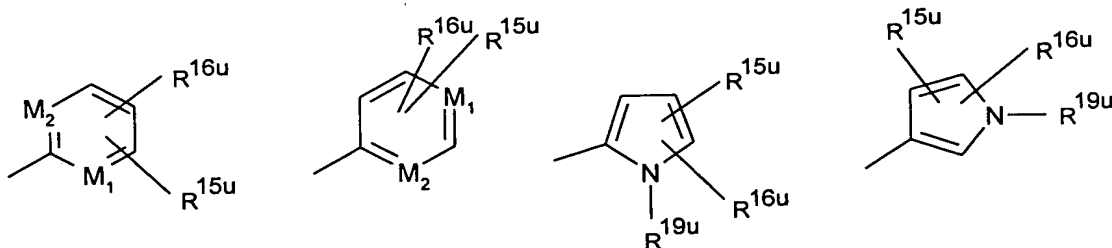
R^{11u} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

- 5 R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is $-OH$, $-NHR^{20u}$ or C_{1-6} -alkoxy wherein R^{20u} is hydrogen or C_{1-6} -alkyl; and R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and R^{14u} is hydrogen or C_{1-6} -alkyl; and

C is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; and

- 10 --- is optionally a single bond or a double bond; and

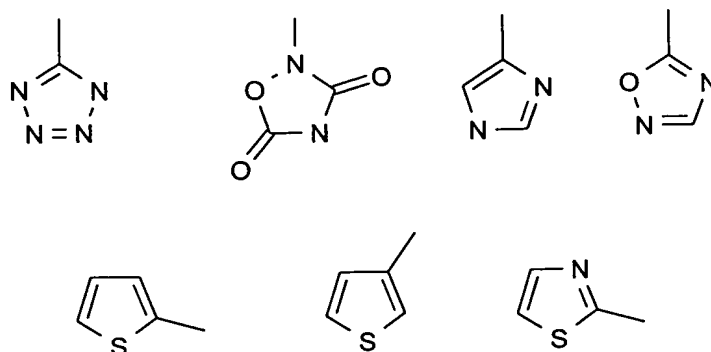
R^{18u} is selected from



wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

- 15 R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or R^{16u} is selected from



or a pharmaceutically acceptable salt thereof.

5 Further preferred compounds of the invention include:

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

10 1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(2R)-piperidinecarboxylic acid;

15

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2Z)-butenyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propionyl)-(3R)-piperidine-carboxylic acid;

20

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-ethyl)-(3R)-piperidine-carboxylic acid;

25

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2E)-butenyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-methyl-3-oxopropyl)-(3R)-piperidinecarboxylic acid;

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-butyryl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxy-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-dibenzo[b,f]azepin-5-ylmethyl)-1-pentyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Trifluoromethyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-1-piperazinyl)-nicotinic acid;

5 1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-cyclopropylmethyl)-(3R)-piperidinecarboxylic acid;

10 1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-cyclopentylmethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-ethyl)-(3R)-piperidinecarboxylic acid;

15 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-3-oxopropyl)-3-piperidinecarboxylic acid;

20 (R)-1-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-benzyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-butyn-1-yl)-3-piperidinecarboxylic acid

25 (R)-1-((2R)-Methyl-3-(3-methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)1-methylpropyl)-3-piperidinecarboxylic acid;

30 (R)-1-(2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidine-

carboxylic acid;

(R)-1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methyl)-3-piperidinecarboxylic acid;

5 1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-
3-pyrrolidinylacetic acid;

2-(1-(3-(10,11-Dihydrodibenzo[b,f]azepin-5-yl)-(2R)-methylpropyl)-4-piperazinyl)-nicotinic
acid;

10

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)methyl)-1-pentyl)-3-piperidinecarboxylic
acid;

15

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxypropyl)piperazin-1-yl)nicotinic
acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-methyl-3-oxo-propyl)-3-piperidinecarboxylic
acid;

20

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionyl)-4-piperidinecarboxylic acid;

25

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylcarbonyl)-1-benzyl)-3-piperidinecarboxylic
acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-benzyl)-3-piperidinecarboxylic
acid;

30

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-3-oxo-1-propyl)-3-
piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methylpropyl)-4-piperidine-
carboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxy-propyl)-4-piperidinecarboxylic acid;

- 5 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxypropyl)-3-piperidinecarboxylic acid;

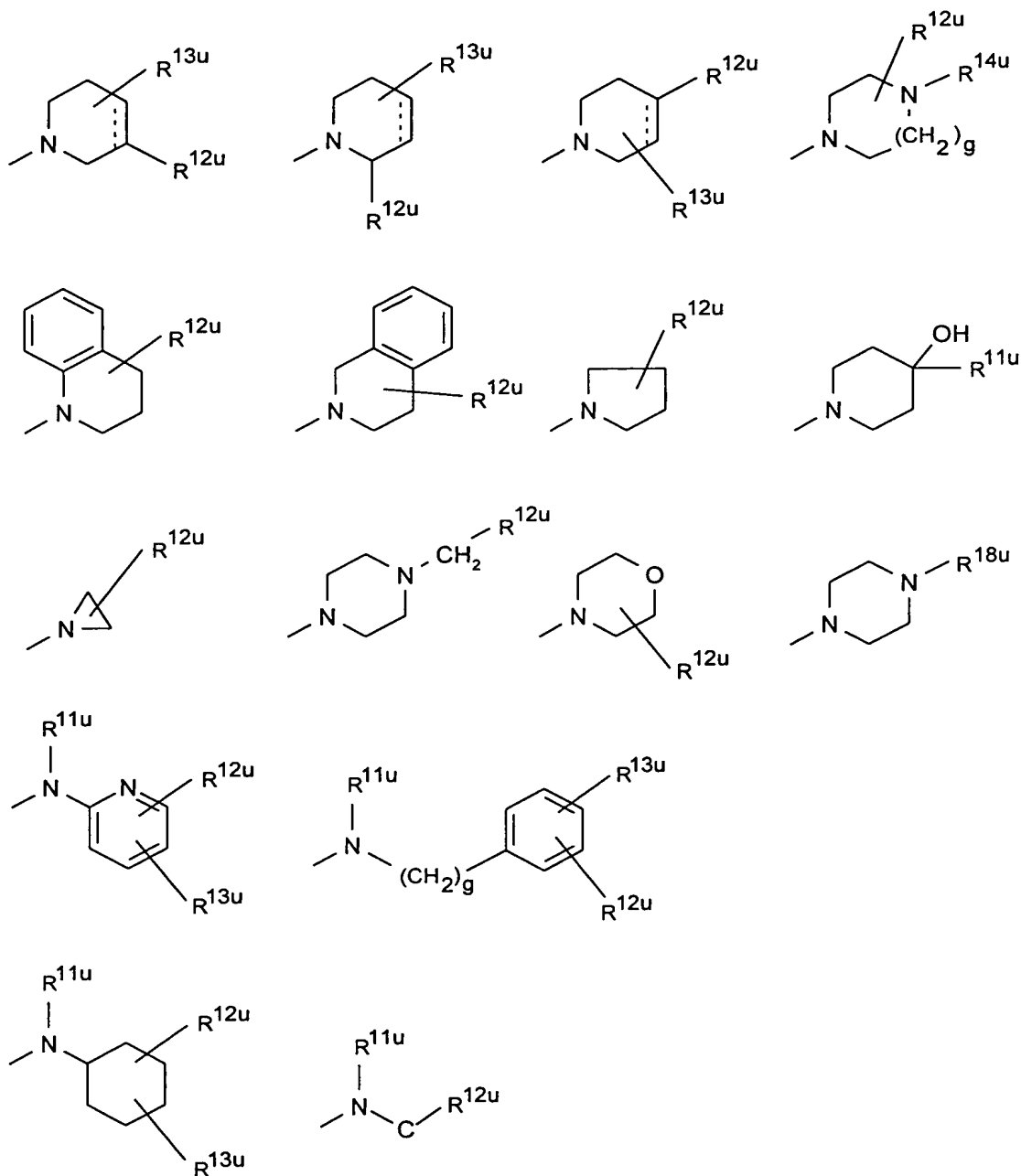
1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-propoxypropyl)-4-piperidinecarboxylic acid;

10

(R)-1-(2-(N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-N-methylamino)ethyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

- 15 R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy or methylthio, -NR⁷R⁸ or -SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and
Y is >CH-O- or >CH-S(O)_y wherein y is 0, 1 or 2, or -N(R⁸)- wherein R⁸ is hydrogen or C₁₋₆-alkyl; and
20 X is completion of an optional bond, ortho-phenylene, -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -CH₂OCH₂-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R⁹)CH₂-, -CH₂CH(R⁹)-, -(C=O)-, -N(R⁸)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and wherein R⁹ is C₁₋₆-alkyl
25 or phenyl; and
p and q independently are 0 or 1; and
r is 1, 2, 3 or 4; and
Z is selected from



wherein g is 0, 1 or 2; and

- 5 R^{11u} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and
 R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and
 wherein R^{17u} is $-OH$, $-NHR^{20u}$ or C_{1-6} -alkoxy wherein R^{20u} is hydrogen or C_{1-6} -alkyl; and

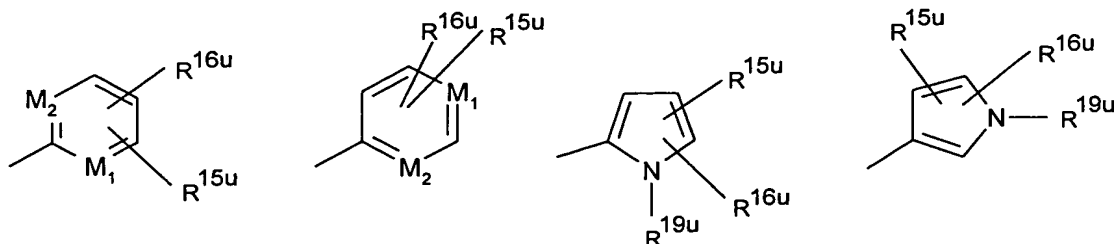
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{14u} is hydrogen or C_{1-6} -alkyl; and

C is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; and

... is optionally a single bond or a double bond; and

5 R^{18u} is selected from



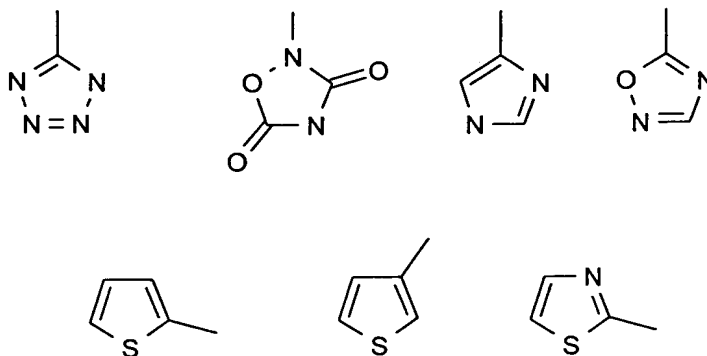
wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

10 R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



15 or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

20 1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

10 1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

15 1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

20 (R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

25 (R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

30 (R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

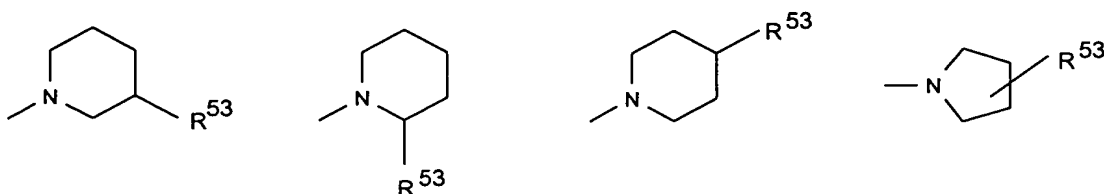
Y is $\text{>N-CH}_2\text{-}$, $\text{>CH-CH}_2\text{-}$ or >C=CH- wherein only the underscored atom participates in the ring system; and

X is ortho-phenylene, -O-, -S-, $\text{-C(R}^7\text{R}^8\text{)-}$, $\text{-CH}_2\text{CH}_2\text{-}$, $\text{-CH=CH-CH}_2\text{-}$, $\text{-CH}_2\text{-CH=CH-}$, $\text{-CH}_2\text{-(C=O)-}$, $\text{-(C=O)-CH}_2\text{-}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{-}$, -CH=CH- , $\text{-N(R}^8\text{)-(C=O)-}$, $\text{-(C=O)-N(R}^8\text{)-}$, $\text{-O-CH}_2\text{-}$, $\text{-CH}_2\text{-O-}$, $\text{-OCH}_2\text{O-}$, $\text{-S-CH}_2\text{-}$, $\text{-CH}_2\text{-S-}$, $\text{-(CH}_2\text{)N(R}^8\text{)-}$, $\text{-N(R}^8\text{)(CH}_2\text{)-}$, $\text{-N(CH}_3\text{)SO}_2\text{-}$, $\text{-SO}_2\text{N(CH}_3\text{)-}$, $\text{-CH(R}^9\text{)CH}_2\text{-}$, $\text{-CH}_2\text{CH(R}^9\text{)-}$, -(C=O)- , $\text{-N(R}^8\text{)-}$ or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

10 Z is selected from



wherein R^{53} is $\text{-(CH}_2\text{)}_{pp}\text{COOH}$ wherein pp is 2, 3, 4, 5 or 6; or a pharmaceutically acceptable salt thereof.

15

Further preferred compounds of the invention include:

3-(1-(3-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-3-yl)propionic acid;

20

3-(1-(3-(10,11-Dihydrodibenzo[b,f]azepin-5-yl)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(2-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)ethyl)piperidin-4-yl)propionic acid;

25

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)piperidin-4-yl)propionic acid;

30

3-(1-(3-(Thioxanthen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(Xanthen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

5

4-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)-butyric acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-2-yl)-propionic acid;

10

3-(1-(3-(1-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

15

3-(1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Trifluoromethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-piperidin-4-yl)propionic acid;

20

3-(1-(3-(2-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

25

3-(1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-piperidin-4-yl)propionic acid;

30

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Fluoro-6,11-dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)-propionic acid;

5 4-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)butyric acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-2-yl)propionic acid;

10

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)-propionic acid;

4-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)-

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butyric acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(10H-Anthracen-9-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

20

3-(1-(3-(Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(10H-Anthracen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

25

3-(1-(3-(Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

5-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)piperidin-4-yl)pentanoic acid;

30

5-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(Thioxanthen-9-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid.

In another preferred embodiment of the invention in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or

5 C_{1-6} -alkoxy; and

Y is $>\underline{N}$ -CH₂-, $>\underline{CH}$ -CH₂-, $>\underline{C}$ =CH- or $>\underline{CH}$ -O- wherein only the underscored atom participates in the ring system; and

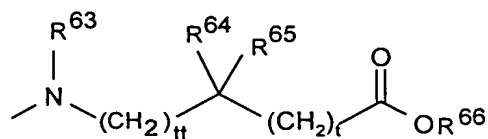
X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH₂-, -CH₂-

10 O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R^8)-, -N(R^8)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R^9)CH₂-, -CH₂CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

15 Z is



wherein tt and t independently are 0, 1 or 2; and

20 R^{63} is H, C_{1-6} -alkyl or optionally substituted benzyl;

R^{64} and R^{65} independently are H, C_{1-8} -alkyl, C_{3-7} -cycloalkyl, phenyl, thienyl, benzyl, or R^{64} and R^{65} together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring; and

R^{66} is H or C_{1-6} -alkyl; or

25 a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic
30 acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

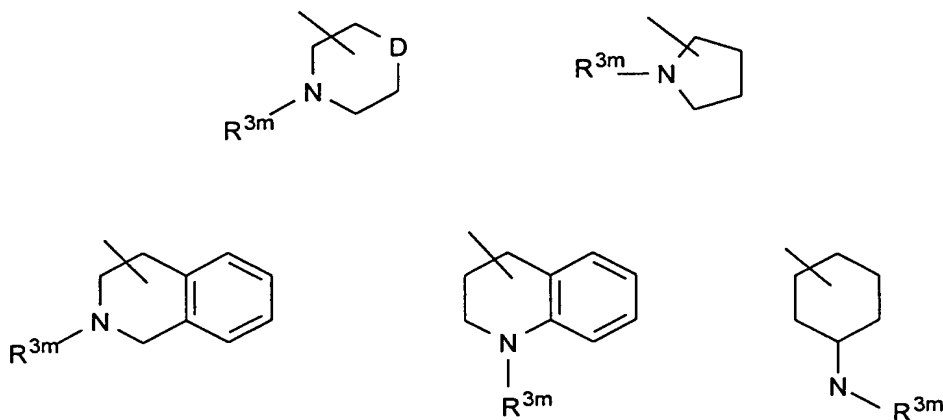
(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

Y is $>\underline{N}-CH_2-$, $>\underline{CH}-CH_2-$ or $>\underline{C}=CH-$ wherein only the underscored atom participates in the ring system; and

- 5 X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R^8)-, -N(R^8)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R^9)CH₂-, -CH₂CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and
- 10 p and q are 0; and
r is 0, 1 or 2; and
Z is selected from



- 15 wherein D is -CH₂-, -O-, -S- or -N(R^7)- wherein R^7 is H or C_{1-6} -alkyl; and
 R^{3m} is $-(CH_2)_{mm}OH$ or $-(CH_2)_{mp}COR^4$ wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH₂, NHOH or C_{1-6} -alkoxy; or
a pharmaceutically acceptable salt thereof.

- 20 Further preferred compounds of the invention include:

3-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-pyrrolidin-1-yl)-propionic acid;

- 25 (2-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-morpholin-4-yl)-acetic acid;

(3-(10,11-Dihydro-5H-dibenz[(b,f)azepin-5-ylmethyl)-1-piperidyl)acetic acid.

In another preferred embodiment of the invention in formula Ia

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R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, cyano, trifluoromethyl, methylthio, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

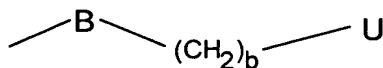
Y is $>\underline{N}$ -, $>\underline{C}H$ -, $>\underline{N}-(C=O)$ - or $>\underline{C}=C(R^8)$ -, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6} -alkyl; and

10 X is ortho-phenylene, -O-, -S-, $-C(R^7R^8)$ -, $-CH_2CH_2$ -, $-CH=CH-CH_2$ -, $-CH_2-CH=CH$ -, $-CH_2-(C=O)$ -, $-(C=O)-CH_2$ -, $-CH_2CH_2CH_2$ -, $-CH=CH$ -, $-N(R^8)-(C=O)$ -, $-(C=O)-N(R^8)$ -, $-O-CH_2$ -, $-CH_2-O$ -, $-OCH_2O$ -, $-CH_2OCH_2$ -, $-S-CH_2$ -, $-CH_2-S$ -, $-(CH_2)N(R^8)$ -, $-N(R^8)(CH_2)$ -, $-N(CH_3)SO_2$ -, $-SO_2N(CH_3)$ -, $-CH(R^9)CH_2$ -, $-CH_2CH(R^9)$ -, $-(C=O)$ -, $-N(R^8)$ - or $-(S=O)$ - wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

15 p and q are 0; and

r is 0, 1, 2, 3 or 4; and

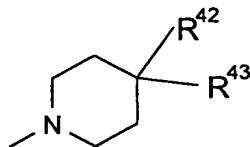
Z is



20 wherein b is 0, 1, 2, 3 or 4; and

B is $-CH=CR^{49}$ -, $-CR^{49}=CH$ -, $-C\equiv C$ -, $-(C=O)$ -, $-(C=CH_2)$ -, $-(CR^{49}R^{40})$ -, $-CH(OR^{41})$ -, $-CH(NHR^{41})$ -, phenylene, C_{3-7} -cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C_{1-6} -unbranched alkyl, C_{3-6} -branched alkyl or C_{3-7} -cycloalkyl and wherein R^{41} is hydrogen or C_{1-6} -alkyl; and

25 U is



wherein R^{42} is hydrogen, $-(CH_2)_cOH$ or $-(CH_2)_dCOR^{47}$ wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R^{47} is $-OH$, $-NHR^{44}$ or C_{1-6} -alkoxy wherein R^{44} is hydrogen or C_{1-6} -alkyl; and

R^{43} is cyano, $-NR^{45}R^{46}$, $-NR^{45}-V$ or $-(CHR^{48})_e-V$ wherein R^{45} and R^{46} independently are hydrogen or C_{1-6} -alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R^{48} is hydrogen, halogen, cyano, trifluoromethyl, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-NR^{45}R^{46}$ or $-COOH$, and wherein V is C_{3-8} -cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C_{1-6} -alkyl or C_{1-6} -alkoxy; or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-phenyl-4-piperidinecarboxylic acid;

4-(4-Chlorophenyl)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

4-(4-Methylphenyl)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-anilino-4-piperidinecarboxamide;

2-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidyl)-2-phenylacetonitrile;

2-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidiny)-2-phenylacetic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-cyano-4 piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ib

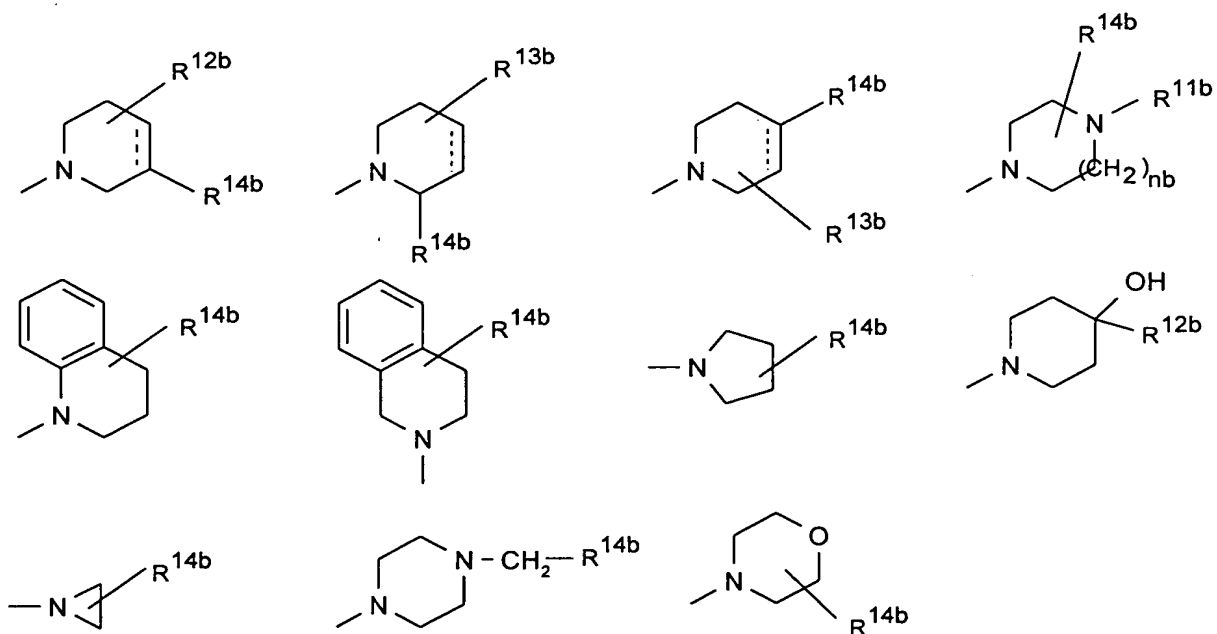
R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{3b} is hydrogen or C_{1-3} -alkyl; and

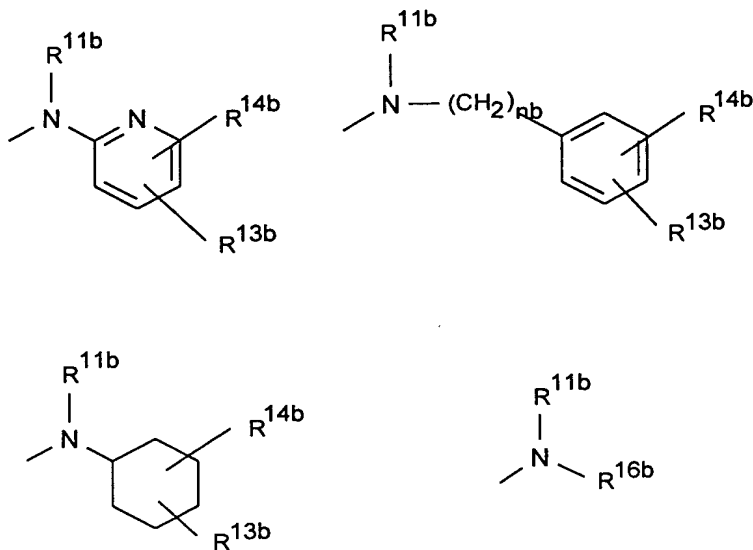
5 A_b is C_{1-3} -alkylene; and

Y_b is $>\underline{C}H-CH_2-$, $>\underline{C}=CH-$, $>\underline{C}H-O-$, $>\underline{C}=N-$, $>\underline{N}-CH_2-$ wherein only the underscored atom participates in the ring system; and

Z_b is selected from



10



wherein nb is 1 or 2; and

R^{11b} is hydrogen or C₁₋₆-alkyl; and

5 R^{12b} is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

R^{14b} is -(CH₂)_{mb}OH or -(CH₂)_{tb}COR^{15b} wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and wherein R^{15b} is -OH, NH₂, -NHOH or C₁₋₆-alkoxy; and

10 R^{16b} is C₁₋₆-alkyl or -B_b-COR^{15b}, wherein B_b is C₁₋₆-alkylene, C₂₋₆-alkenylene or C₂₋₆-alkynylene and R^{15b} is the same as above; and

... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

15 Further preferred compounds of the invention include:

2-Chloro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(2-dimethylamino)ethoxy-12H-dibenzo[d,g][1,3]dioxocine;

20

2,10-Dichloro-12-(3-dimethylamino)propyl-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(3-dimethylamino-1-methyl)ethoxy-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(2-dimethylaminopropylidene)-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

5

3-Chloro-12-(3-dimethylamino-1-methylpropylidene)-12H-dibenzo[d,g][1,3]dioxocine;

2-Fluoro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

10 2-Methyl-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

2-Chloro-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

15

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)propyl)-3-piperidinecarboxylic acid ethyl ester;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)propyl)-3-piperidinecarboxylic acid.

20

In another preferred embodiment of the invention in formula Ic

R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

25

X_c is ortho-phenylene, -O-, -S-, -C($R^{6c}R^{7c}$)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R^{8c})-(C=O)-, -(C=O)-N(R^{8c})-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R^{8c})-, -N(R^{8c})(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R^{10c})CH₂-, -CH₂CH(R^{10c})-, -(C=O)-, -N(R^{9c})- or -(S=O)- wherein R^{6c} , R^{7c} , R^{8c} and R^{9c} independently are hydrogen or C_{1-6} -alkyl, and wherein R^{10c} is C_{1-6} -alkyl or phenyl; and

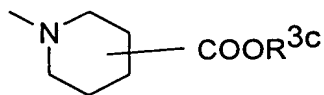
30

Y_c is C or N; and

... is optionally a single bond or a double bond, and ... is a single bond when Y_c is N; and

m_c is 1, 2, 3, 4, 5 or 6; and

Z_c is -COOR^{3c} or



wherein R^{3c} is H or C₁₋₆-alkyl; or
a pharmaceutically acceptable salt thereof.

5

Further preferred compounds of the invention include:

1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

10

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidine-carboxylic acid;

15

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidine-carboxylic acid;

20

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

25

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

30

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid.

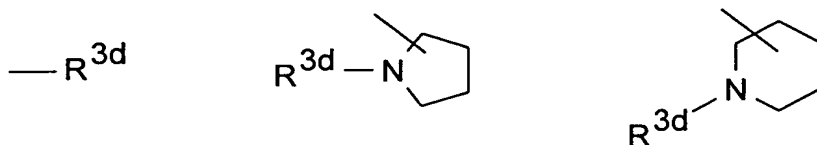
10 In another preferred embodiment of the invention in formula Id

R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

X_d is -O-, -S- or -S(=O)-; and

15 rd is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ; and

Z_d is selected from



wherein R^{3d} is $-(CH_2)_{md}OH$ or $-(CH_2)_{pd}COR^{4d}$ wherein md and pd independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2 , $NHOH$ or C_{1-6} -alkoxy; or
 20 a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

25 4-(1,3,4,14b-Tetrahydro-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]oxazepin-2-yl)-butanoic acid;

4-(1,3,4,14b-Tetrahydro-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]thiazepin-2-yl)-butanoic acid.

The compounds of general formulas Ia-IId may be prepared by using the methods taught in
 30 WO9631497, WO9631498, WO9631499, WO9631481, WO9711071, WO9815548,

WO9815546, WO9815550, PCT/DK98/00273, PCT/DK98/00271, DK 0367/98, DK 0366/98, DK 1472/97 and DK 1523/98, which are hereby incorporated by reference.

It has been demonstrated that the compounds of the present the invention can be used in the treatment of indications related to angiogenesis according to the following experiment.

PHARMACOLOGICAL METHODS

The effects of compounds of formulas Ia-IId on angiogenesis is suggested by the following experiment. Air pouches were formed on the dorsum of female To mice and were inflamed one day later by injection of 0.5 ml Freund's complete adjuvant supplemented with 0.1% croton oil. Animals were dosed with compounds of formulas Ia-IId given via the drinking water equivalent to 0.3-3 mg/kg/day. Control animals received normal drinking water. After 6 days the animals received an injection of carmine in gelatine intravenously prior to dissection of the air pouch granuloma. A comparison of granuloma dry weight, carmine content and vascular index (carmine content/granuloma dry weight) was made between the groups (Colville-Nash et al., J. Pharmacol. Exp. Ther. 274 1463-1472, 1995).

PHARMACEUTICAL COMPOSITIONS

The present invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds according to the invention or a pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions comprising a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound according to the invention or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the

compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, syrup, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, topical, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound according to the invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 g
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	

Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of indications related to angiogenesis. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, in an effective amount.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of humans, dosages from about 0.1 to about 1000 mg, preferably from about 0.5 to about 500 mg of compounds of formula I, conveniently given from 1 to 5 times daily. A most preferable dosage is from about 50 to about 200 mg per dose when administered to e.g. a human. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 50 to about 200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

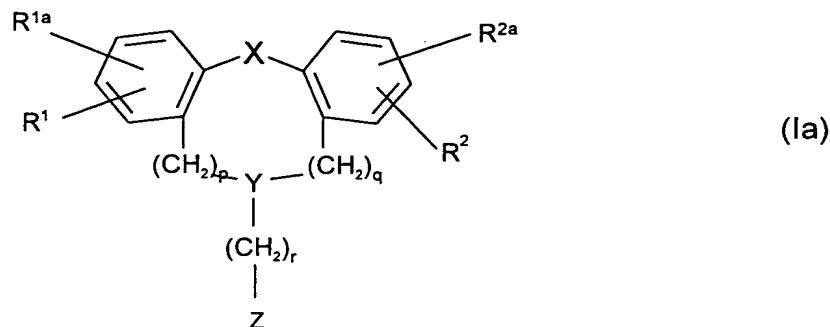
Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.1 mg to about 1000 mg, preferably from about 0.5 mg to about 500 mg of the compounds according to the invention admixed with a pharmaceutically acceptable carrier or diluent.

The method of treating may be described as the treatment, prevention, elimination, alleviation or amelioration of an indication related to angiogenesis in a subject in need thereof, which comprises the step of administering to the said subject an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

Any novel feature or combination of features described herein is considered essential to this invention.

CLAIMS

1. The use of a compound having the general formula Ia



wherein R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6} -alkyl, C_{1-6} -alkoxy, hydroxy, NR^7R^8 , cyano, methylthio or $-SO_2NR^7R^8$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and

Y is $>\underline{N}-CH_2-$, $>\underline{CH}-CH_2-$ or $>\underline{C}=\underline{CH}-$ wherein only the underscored atom participates in the ring system; or

Y is $-\underline{CH}_2\underline{N}(-)CH_2-$, $-\underline{CH}_2\underline{N}(-)\underline{CH}_2-$, $-(\underline{C}=\underline{O})\underline{N}(-)CH_2-$, $-\underline{CH}_2\underline{N}(-)(\underline{C}=\underline{O})-$, $-\underline{CH}_2\underline{CH}(-)CH_2-$, $-\underline{CH}_2\underline{CH}(-)\underline{CH}_2-$, $-\underline{CH}_2\underline{C}(-)=CH-$, $-\underline{CH}=\underline{C}(-)\underline{CH}_2-$, $-\underline{OCH}(-)CH_2-$, $-\underline{CH}_2\underline{CH}(-)\underline{O}-$, $-\underline{SCH}(-)CH_2-$, $-\underline{CH}_2\underline{CH}(-)\underline{S}-$, wherein only the underscored atom participates in the ring system; or

Y is $>\underline{N}-$, $>\underline{CH}-$, $>\underline{N}-(\underline{C}=\underline{O})-$ or $>\underline{C}=\underline{C}(R^8)-$, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6} -alkyl; or

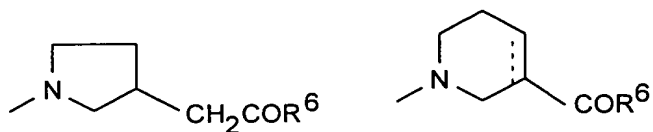
Y is $>\underline{CH}-O-$ or $>\underline{CH}-S(O)_y$, wherein y is 0, 1 or 2, or $-N(R^8)-$ wherein R^8 is hydrogen or C_{1-6} -alkyl, and wherein only the underscored atom participates in the ring system; and

X is completion of an optional bond, ortho-phenylene, $-O-$, $-S-$, $-C(R^7R^8)-$, $-CH_2CH_2-$, $-CH=CH-$, $-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(\underline{C}=\underline{O})-$, $-(\underline{C}=\underline{O})-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(\underline{C}=\underline{O})-$, $-(\underline{C}=\underline{O})-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-CH_2OCH_2-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^9)CH_2-$, $-CH_2CH(R^9)-$, $-(\underline{C}=\underline{O})-$, $-N(R^8)-$ or $-(S=\underline{O})-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

p and q independently are 0 or 1; and

r is 0, 1, 2, 3 or 4; and

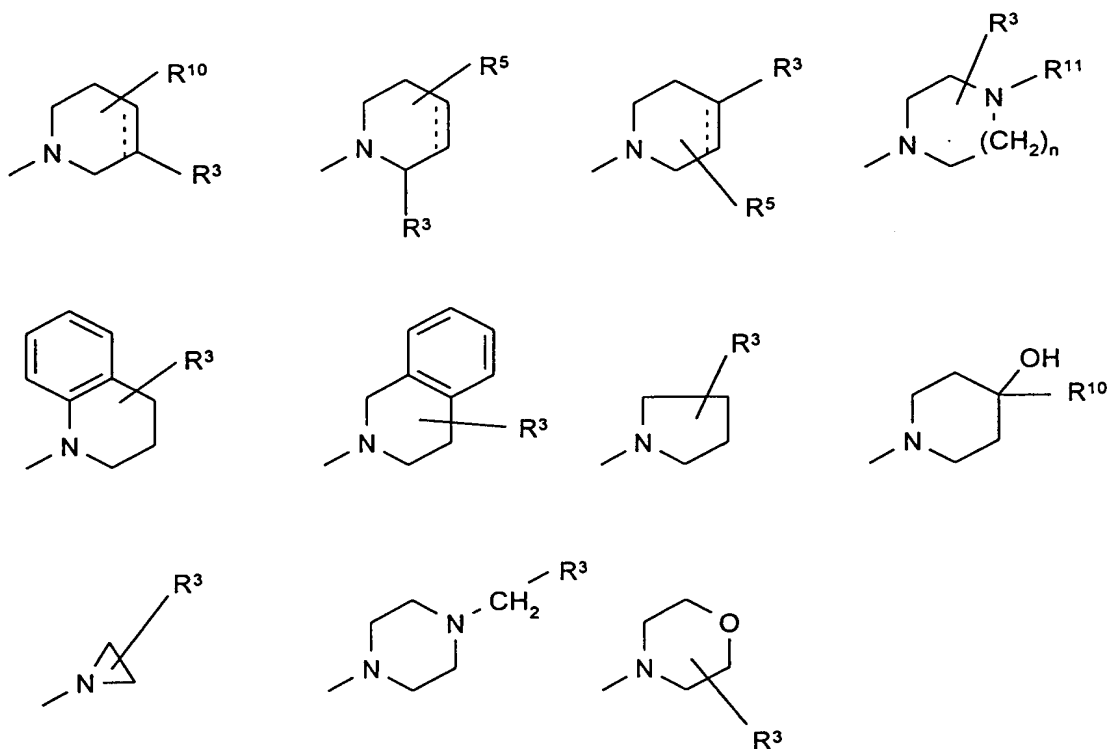
5 Z is selected from



wherein R^6 is OH or C_{1-6} -alkoxy; and

... is optionally a single bond or a double bond; or

10 Z is selected from



wherein n is 1 or 2;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

15 R^4 is -OH, -NH₂, -NHOH or C_{1-6} -alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

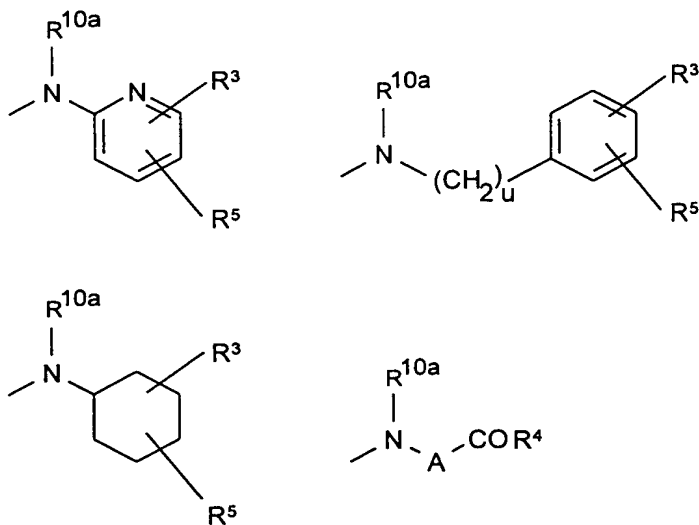
R^{10} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{11} is hydrogen or C_{1-6} -alkyl; and

... is optionally a single bond or a double bond; or

5

Z is selected from



10 wherein u is 0 or 1;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

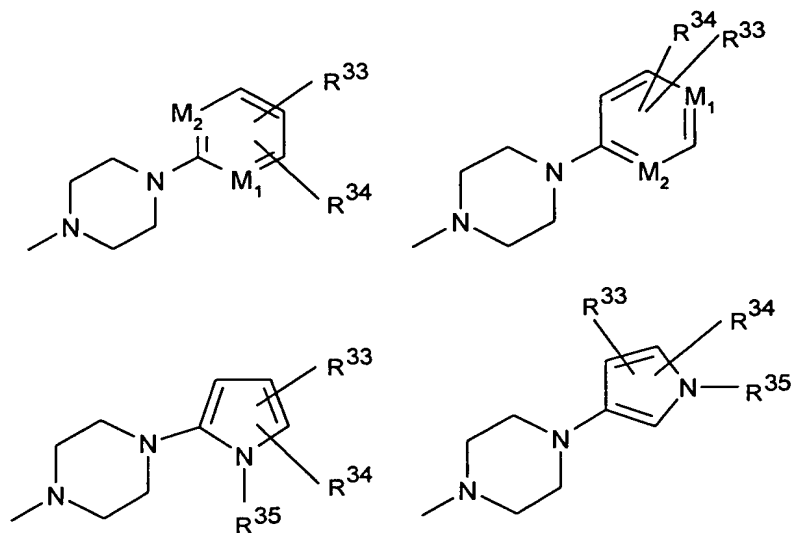
R^4 is $-OH$, $-NH_2$, $-NHOH$ or C_{1-6} -alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{10a} is hydrogen or C_{1-6} -alkyl; and

15 A is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; or

Z is selected from



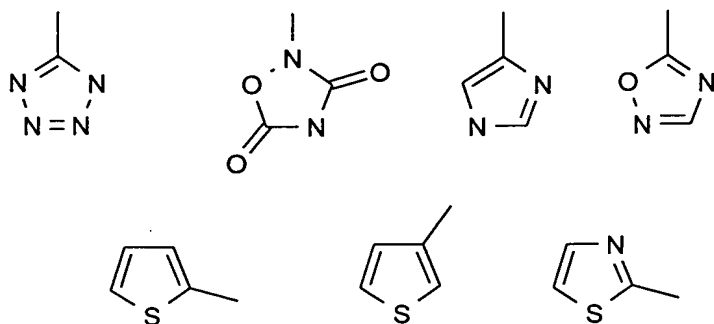
wherein M_1 and M_2 independently are C or N; and

R^{35} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

5 R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6} -alkoxy or NHR^{32} , wherein R^{32} is hydrogen or C_{1-6} -alkyl, and w is 0, 1 or 2; or

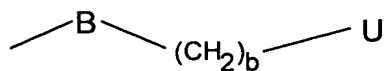
R^{34} is selected from



10

; or

Z is

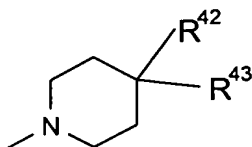


15

wherein b is 0, 1, 2, 3 or 4; and

B is $-\text{CH}=\text{CR}^{49}-$, $-\text{CR}^{49}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-(\text{C}=\text{O})-$, $-(\text{C}=\text{CH}_2)-$, $-(\text{CR}^{49}\text{R}^{40})-$, $-\text{CH}(\text{OR}^{41})-$, $-\text{CH}(\text{NHR}^{41})-$, phenylene, C_{3-7} -cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C_{1-6} -unbranched alkyl, C_{3-6} -branched alkyl or C_{3-7} -cycloalkyl and wherein R^{41} is hydrogen or C_{1-6} -alkyl; and

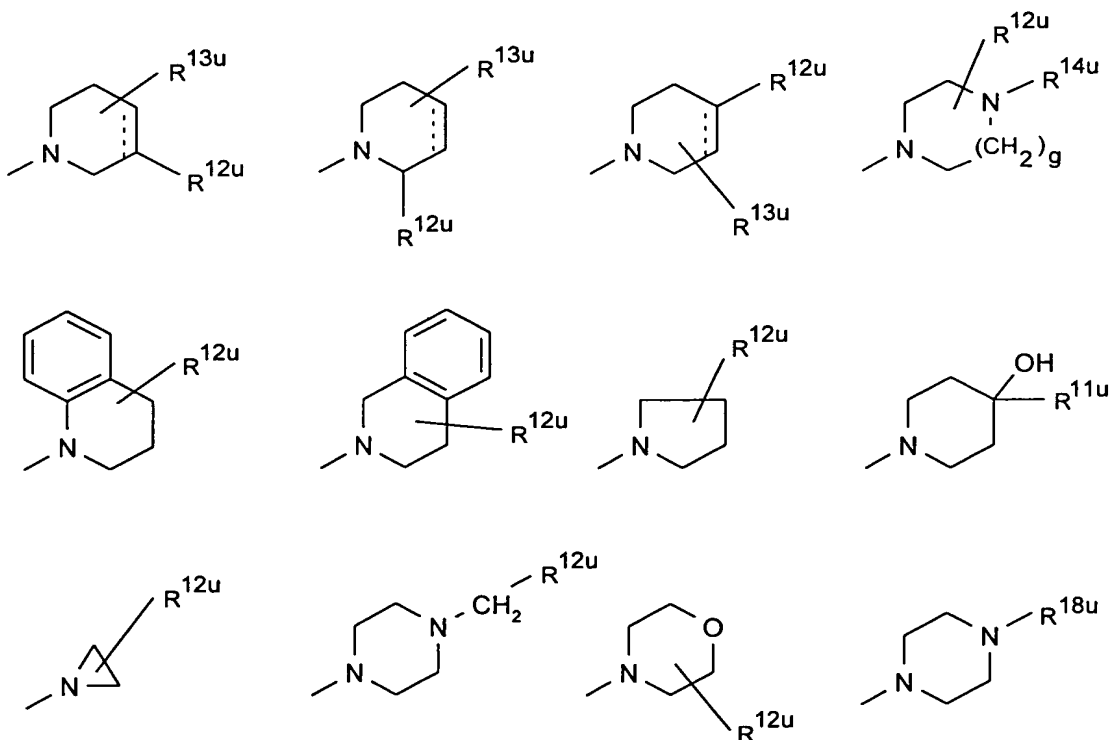
5 U is

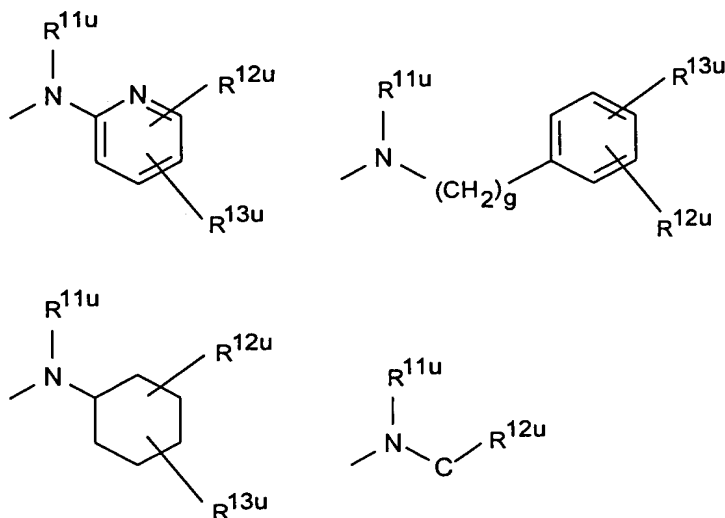


wherein R^{42} is hydrogen, $-(\text{CH}_2)_c\text{OH}$ or $-(\text{CH}_2)_d\text{COR}^{47}$ wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R^{47} is $-\text{OH}$, $-\text{NHR}^{44}$ or C_{1-6} -alkoxy wherein R^{44} is hydrogen or C_{1-6} -alkyl; and

10 R^{43} is cyano, $-\text{NR}^{45}\text{R}^{47}$, $-\text{NR}^{45}-\text{V}$ or $-(\text{CHR}^{48})_e-\text{V}$ wherein R^{45} and R^{47} independently are hydrogen or C_{1-6} -alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R^{48} is hydrogen, halogen, cyano, trifluoromethyl, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-\text{NR}^{45}\text{R}^{47}$ or $-\text{COOH}$, and wherein V is C_{3-8} -cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C_{1-6} -alkyl or C_{1-6} -alkoxy; or

15 U is selected from





wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is $-OH$, $-NHR^{20u}$ or C_{1-6} -alkoxy wherein R^{20u} is hydrogen or C_{1-6} -alkyl; and

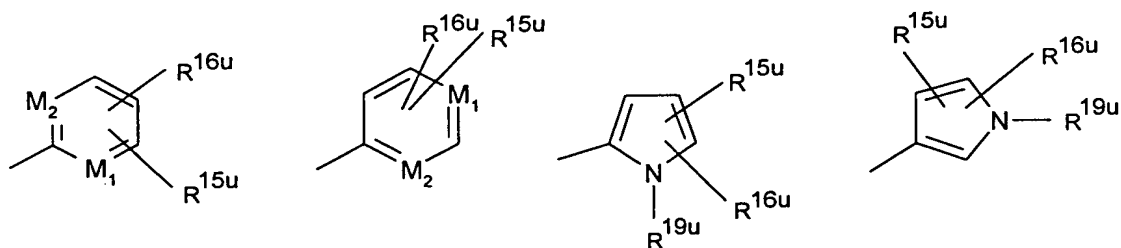
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{14u} is hydrogen or C_{1-6} -alkyl; and

C is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; and

... is optionally a single bond or a double bond; and

R^{18u} is selected from



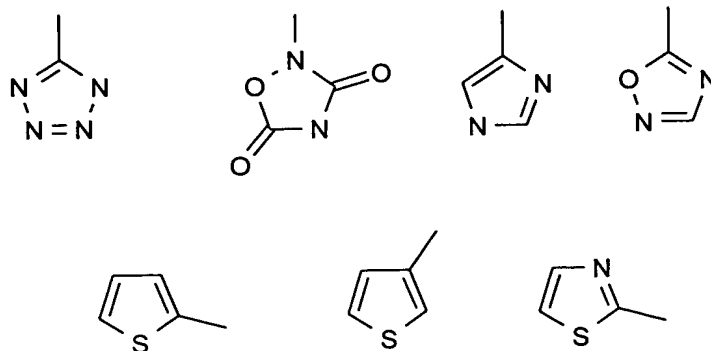
wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

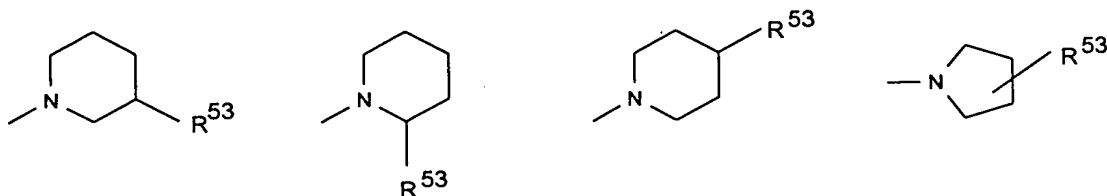
R^{16u} is selected from



; or

5

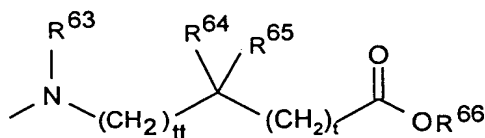
Z is selected from



wherein R^{53} is $-(CH_2)_{pp}COOH$ wherein pp is 2, 3, 4, 5 or 6; or

10

Z is



wherein tt and t independently are 0, 1 or 2; and

15 R^{63} is H, C_{1-6} -alkyl or optionally substituted benzyl;

R^{64} and R^{65} independently are H, C_{1-8} -alkyl, C_{3-7} -cycloalkyl, phenyl, thienyl, benzyl, or R^{64} and

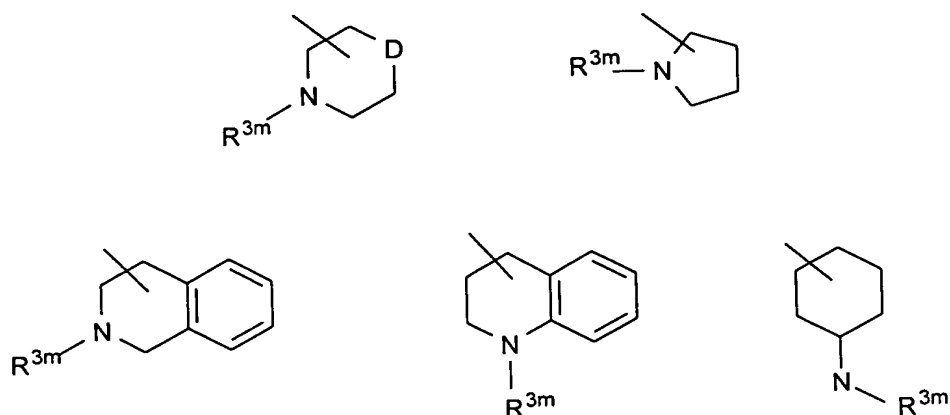
R^{65} together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring;

and

R^{66} is H or C_{1-6} -alkyl; or

20

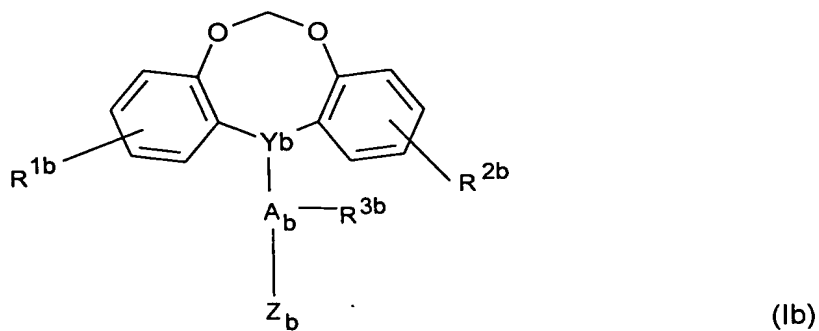
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wherein D is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$ or $-\text{N}(\text{R}^7)-$ wherein R^7 is hydrogen or C_{1-6} -alkyl; and R^{3m} is $-(\text{CH}_2)_{mm}\text{OH}$ or $-(\text{CH}_2)_{mp}\text{COR}^4$ wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH_2 ,

5 NHOH or C_{1-6} -alkoxy; or

having the general formula Ib

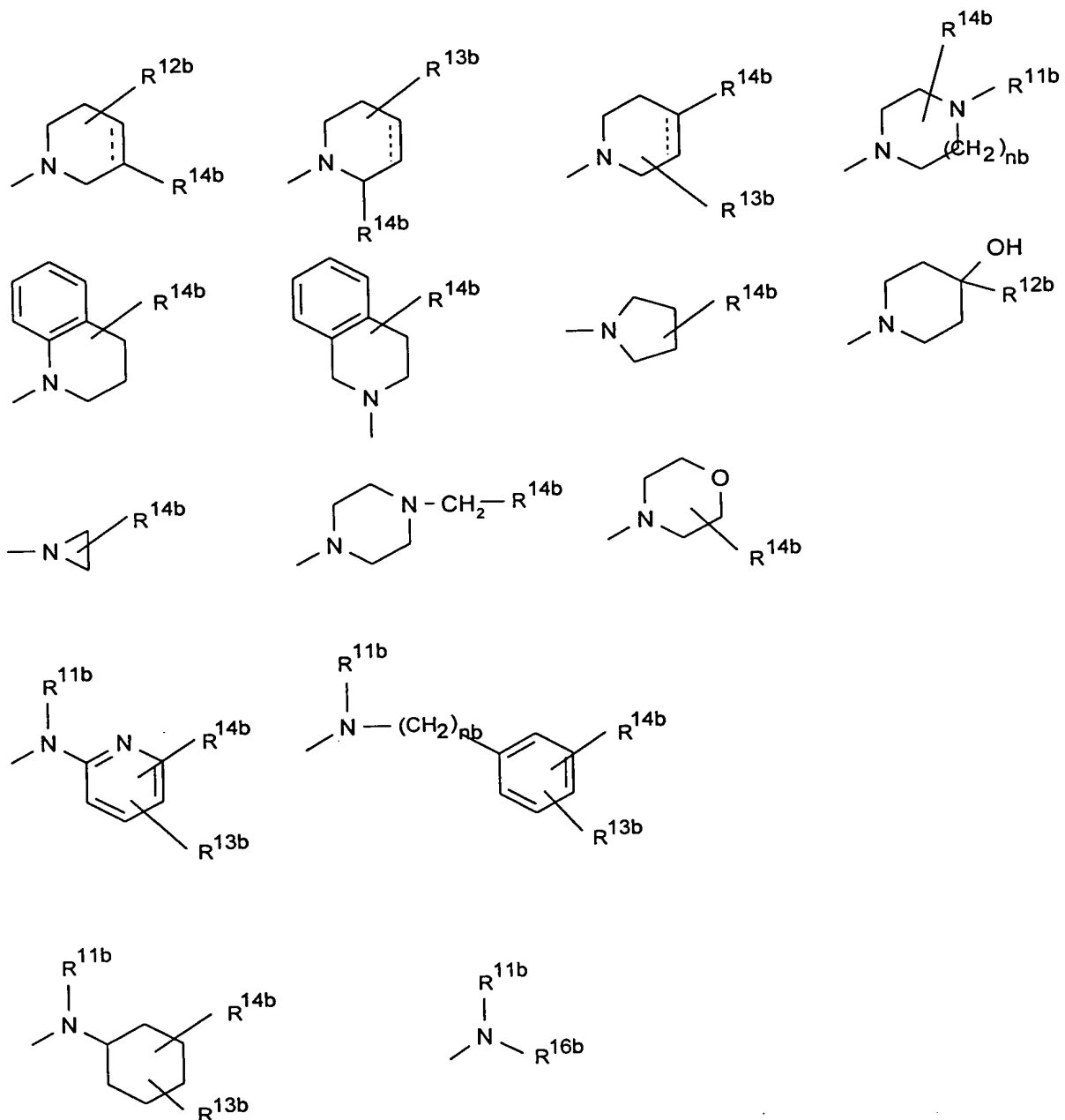


10 wherein R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{3b} is hydrogen or C_{1-3} -alkyl; and

A_b is C_{1-3} -alkylene; and

15 Y_b is $>\underline{\text{C}}\text{H}-\text{CH}_2-$, $>\underline{\text{C}}=\text{CH}-$, $>\underline{\text{C}}\text{H}-\text{O}-$, $>\underline{\text{C}}=\text{N}-$, $>\underline{\text{N}}-\text{CH}_2-$ wherein only the underscored atom participates in the ring system; and Z_b is selected from

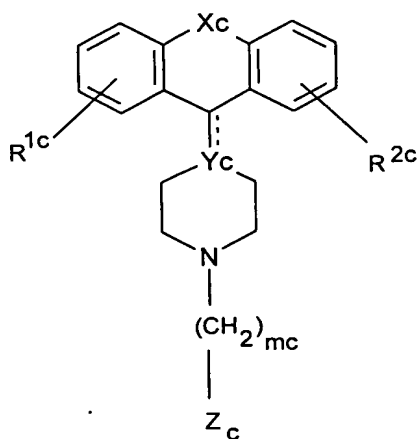


- 5 wherein nb is 1 or 2; and
 R^{11b} is hydrogen or C₁₋₆-alkyl; and
 R^{12b} is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or phenyl optionally substituted with halogen, trifluoro-
 methyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and
 R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and
 10 R^{14b} is $-(CH_2)_{mb}OH$ or $-(CH_2)_{tb}COR^{15b}$ wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and
 wherein R^{15b} is -OH, NH₂, -NHOH or C₁₋₆-alkoxy; and

R^{16b} is C_{1-6} -alkyl or $-B_b-COR^{15b}$, wherein B_b is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene and R^{15b} is the same as above; and

... is optionally a single bond or a double bond; or

5 having the general formula Ic



wherein R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or

10 C_{1-6} -alkoxy;

X_c is ortho-phenylene, -O-, -S-, $-C(R^{6c}R^{7c})-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-$
 $(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^{8c})-(C=O)-$, $-(C=O)-N(R^{8c})-$, $-O-CH_2-$, $-CH_2-$
 O-, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^{8c})-$, $-N(R^{8c})(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-$
 $CH(R^{10c})CH_2-$, $-CH_2CH(R^{10c})-$, $-(C=O)-$, $-N(R^{9c})-$ or $-(S=O)-$ wherein R^{6c} , R^{7c} , R^{8c} and R^{9c} inde-

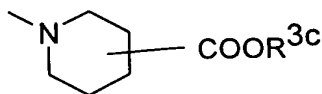
15 pendently are hydrogen or C_{1-6} -alkyl, and wherein R^{10c} is C_{1-6} -alkyl or phenyl;

Y_c is C or N;

... is optionally a single bond or a double bond, and ... is a single bond when Y_c is N;

mc is 1, 2, 3, 4, 5 or 6; and

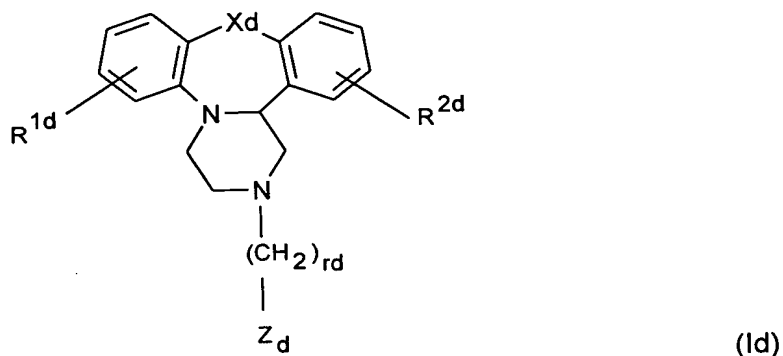
Z_c is $-COOR^{3c}$ or



20

wherein R^{3c} is H or C_{1-6} -alkyl; or

having the general formula Id



5

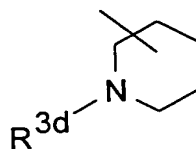
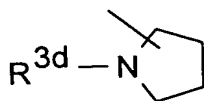
wherein R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

X_d is -O-, -S- or -S(=O)-; and

r_d is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10; and

10

Z_d is selected from



wherein R^{3d} is $-(CH_2)_{m_d}OH$ or $-(CH_2)_{p_d}COR^{4d}$ wherein m_d and p_d independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2 , $NHOH$ or C_{1-6} -alkoxy; or

15

a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of an indication related to angiogenesis.

2. The use according to claim 1 wherein angiogenesis is related to cancer.

3. The use according to anyone of the claims 1-2 wherein in formula Ia

20

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

Y is $>\underline{N}-CH_2-$, $>\underline{CH}-CH_2-$ or $>\underline{C}=CH-$ wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -O-CH₂-, -(C=O)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and

p and q are 0, and

5 r is 1, 2 or 3; and

Z is selected from



wherein R⁶ is OH or C₁₋₆-alkoxy; and

... is optionally a single bond or a double bond; or

10 a pharmaceutically acceptable salt thereof.

4. The use according to anyone of the claims 1- 3 wherein the compound is selected from the following:

15 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

20

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

(R)-1-(3-(Fluoren-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

25

1-(3-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(Thioxanthen-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-butyl)-3-piperidinecarboxylic acid;

5

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

10

(R)-1-(3-(10H-Phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

15

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-pyrrolidinacetic acid;

(R)-1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

20

(R)-1-(3-(2-Trifluoromethyl-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Oxo-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

25

(R)-1-(3-(11H-10-Oxa-5-aza-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

30

(R)-1-(3-(6,7-Dihydro-5H-dibenzo[b,g]azocin-12-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10-Methyl-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9(H)-Oxo-10H-acridin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(2-(6,11-Dihydrodibenz[b,e]oxepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(Z)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(E)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride,

5 or a pharmaceutically acceptable salt thereof.

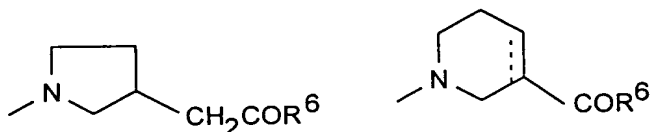
5. The use according to anyone of the claims 1-2 wherein in formula Ia

R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

10 Y is $\text{-}\underline{\text{C}}\text{H}_2\text{N}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\text{CH}_2\text{N}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-(}\underline{\text{C}}=\text{O)}\text{N}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\text{CH}_2\text{N}(\text{-})(\underline{\text{C}}=\text{O})\text{-}$, $\text{-}\underline{\text{C}}\text{H}_2\underline{\text{C}}\text{H}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\text{CH}_2\underline{\text{C}}\text{H}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\underline{\text{C}}\text{H}_2\underline{\text{C}}(\text{-})=\text{CH-}$, $\text{-}\text{CH}=\underline{\text{C}}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\underline{\text{O}}\text{CH}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\text{CH}_2\underline{\text{C}}\text{H}(\text{-})\underline{\text{O}}\text{-}$, $\text{-}\underline{\text{S}}\text{CH}(\text{-})\underline{\text{C}}\text{H}_2\text{-}$, $\text{-}\text{CH}_2\underline{\text{C}}\text{H}(\text{-})\underline{\text{S}}\text{-}$, wherein only the underscored atom participates in the ring system; and
X is -O- , -S- , $\text{-C(R}^7\text{R}^8\text{)-}$, $\text{-CH}_2\text{CH}_2\text{-}$, $\text{-CH=CH-CH}_2\text{-}$, $\text{-CH}_2\text{-CH=CH-}$, $\text{-CH}_2\text{-(C=O)-}$, $\text{-(C=O)-CH}_2\text{-}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{-}$, -CH=CH- , $\text{-N(R}^8\text{)-(C=O)-}$, $\text{-(C=O)-N(R}^8\text{)-}$, $\text{-O-CH}_2\text{-}$, $\text{-CH}_2\text{-O-}$, $\text{-S-CH}_2\text{-}$, $\text{-CH}_2\text{-S-}$, $\text{-N(R}^8\text{)-}$, -(C=O)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and
15 p and q independently are 0 or 1; and

r is 1, 2 or 3; and

Z is selected from



20 wherein R⁶ is OH or C₁₋₆-alkoxy; and

... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

6. The use according to anyone of the claims 1- 2 and 5 wherein the compound is selected from the following:
25

(R)-1-(3-(6,11-Dioxo-6,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6,11-Dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5,11-Dihydro-10H-dibenzo[b,e][1,4]diazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

5

(R)-1-(3-(11H-Dibenzo[b,f][1,4]thiazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenz[b,f][1,4]oxazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

10

(R)-1-(3-(11H-Dibenz[b,f][1,4]oxathiepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenzo[b,e][1,4]dithiepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenz[b,e][1,4]oxathiepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

15

(R)-1-(3-(11,12-Dihydro-10H-dibenz[b,g][1,5]oxazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-10H-dibenzo[b,g][1,5]thiazocin-11-yl)-1-propyl)-3-

20

piperidinecarboxylic acid;

1-(3-(11,12-Dihydro-6H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(11,12-Dihydro-5H-dibenzo[a,e]cycloocten-5-ylidene)-1-propyl)-3-piperidinecarboxylic

25

acid;

1-(3-(6-Oxo-11,12-dihydro-5H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(7,12-Dihydro-6H-dibenzo[a,d]cycloocten-6-ylidene)-1-propyl)-3-piperidinecarboxylic

30

acid;

1-(3-(5-Methyl-5,11-dihydro-dibenz[b,f]azepin-10-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Oxo-5,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11-Oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6-Oxo-11,12-dihydro-5H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-dibenz[b,f][1,4]oxazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5,6,11,12-Tetrahydro-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11-Oxo-6,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Methyl-dibenz[b,f]azepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6,7-Dihydro-5H-dibenz[b,g][1,5]oxazocin-6-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-dibenz[a,e]cycloocten-5-yl)-1-propyl)-3-piperidinecarboxylic acid,

or a pharmaceutically acceptable salt thereof.

7. The use according to anyone of the claims 1-2 wherein in formula Ia

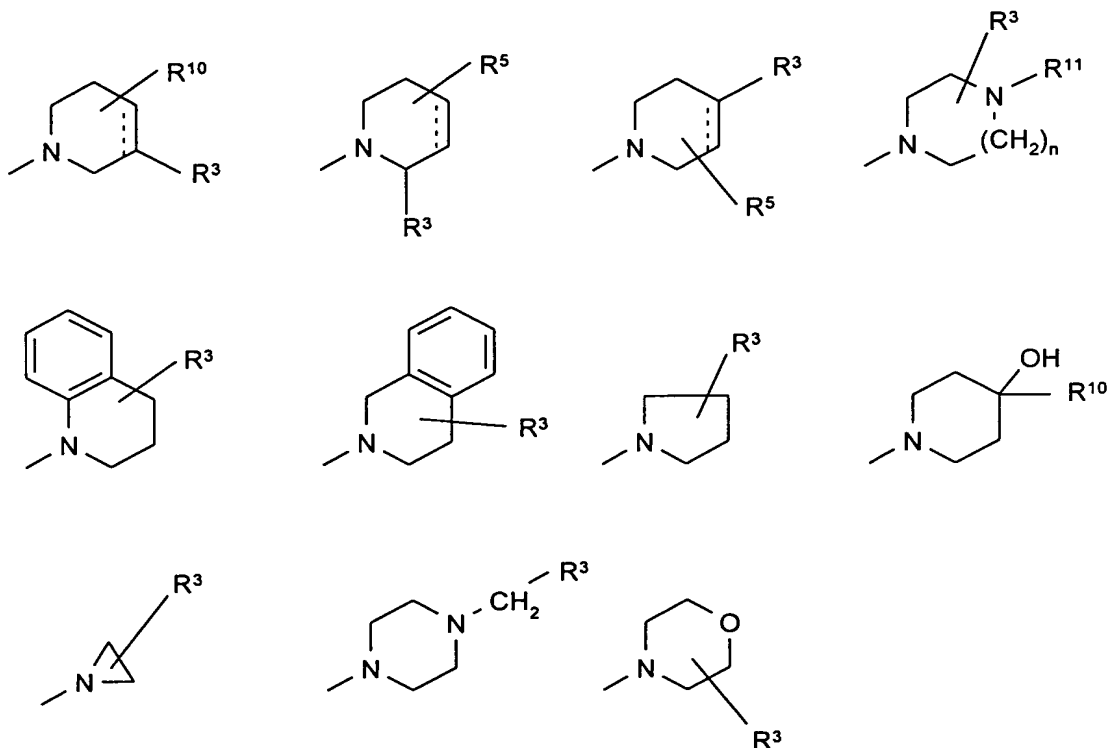
R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, NR⁷R⁸, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and

Y is >N-CH₂-, >CH-CH₂- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -S-CH₂-, -CH₂-S-, -N(R⁸)-, -(C=O)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



wherein n is 1 or 2; and

- 5 R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein R^4 is $-OH$, $-NH_2$, $-NHOH$ or C_{1-6} -alkoxy; and
- R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and
- R^{10} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and
- 10 R^{11} is hydrogen or C_{1-6} -alkyl; and
- _____ is optionally a single bond or a double bond; or
- a pharmaceutically acceptable salt thereof.

8. The use according to anyone of the claims 1- 2 and 7 wherein the compound is selected from the following:
- 15

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidine-carboxamide;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

- 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperidinecarboxylic acid;
- (1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinyloxy)methanol;
- 5 4-(4-Chlorophenyl)-1-(3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinol;
- 4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperazinecarboxylic acid;
- 10 (2S,4R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-hydroxy-2-pyrrolidinecarboxylic acid;
- 4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-morpholinecarboxylic acid;
- 15 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-aziridinecarboxylic acid;
- 2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1,2,3,4-tetrahydro-4-isoquinolinecarboxylic acid;
- 20 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-methyl-[1,4]-diazepane-6-carboxylic acid;
- 2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid;
- 25 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid hydroxamide;
- (4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)piperazin-1-yl)acetic acid;
- 30 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;
- 4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperazinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidineacetic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic
5 acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-
piperidinecarboxamide;

10 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-
pyrrolidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-
pyrrolidinecarboxylic acid;

15 1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic
acid;

1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-4-piperidinecarboxylic acid;

20 1-(3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic
acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidineacetic acid;

25 1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-methyl-3-piperidinecarboxylic
acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-quinuclidiniumcarboxylate;

30 1-(3-(2,8-Dibromo-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic
acid;

1-(3-(3,7-Dichloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

5 1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(3,7-Dimethyl-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

10 1-(3-(3-Dimethylamino-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

15

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

20

1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Chloro-6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

25

1-(2-(2-Chloro-6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

30

1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

5

1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-2-piperidineacetic acid;

10

1-(3-(Phenothiazin-10-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-2-piperidinecarboxylic acid;

15

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]oxepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid,

20

or a pharmaceutically acceptable salt thereof.

9. The use according to anyone of the claims 1-2 wherein in formula Ia

R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

25

Y is >N-CH₂-, >CH-CH₂- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is ortho-phenylene, -CH₂-(C=O)-, -(C=O)-CH₂-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R⁹)CH₂- or -CH₂CH(R⁹)- wherein R⁸ is hydrogen or C₁₋₆-alkyl

30

and R⁹ is C₁₋₆-alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



wherein R^6 is OH or C_{1-6} -alkoxy; and

... is optionally a single bond or a double bond; or
a pharmaceutically acceptable salt thereof.

5

10. The use according to anyone of the claims 1- 2 and 9 wherein the compound is selected from the following:

1-(3-(9H-Tribenz[b,d,f]azepin-9-yl)-1-propyl)-3-piperidinecarboxylic acid;

10

1-(3-(Tribenzo[a,c,e]cyclohepten-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(5-Methyl-5,6-dihydrodibenz[b,e]azepin-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

15

1-(3-(6-Methyl-6H-dibenzo[c,f][1,2]thiazepin-5,5-dioxide-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10-Methyl-10,11-dihydro-5H-dibenzo[b,e]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

20

1-(3-(10-Phenyl-10,11-dihydro-5H-dibenzo[b,e]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6,11-Dihydro-11H-dibenzo[b,e][1,4]thiazepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

25

1-(3-(10-Methyl-10,11-dihydro-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10-Oxo-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

5 (R)-1-(3-(6-Methyl-6,11-dihydro-dibenzo[c,f][1,2,5]thiadiazepin-5,5-dioxide-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Methyl-5,6-dihydrodibenz[b,e]azepin-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

10 (R)-1-(3-(9H-Tribenzo[a,c,e]cyclohepten-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9H-Tribenzo[b,d,f]azepine-9-yl)propyl)-3-piperidinecarboxylic acid,

or a pharmaceutically acceptable salt thereof.

15

11. The use according to anyone of the claims 1-2 wherein in formula Ia

R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

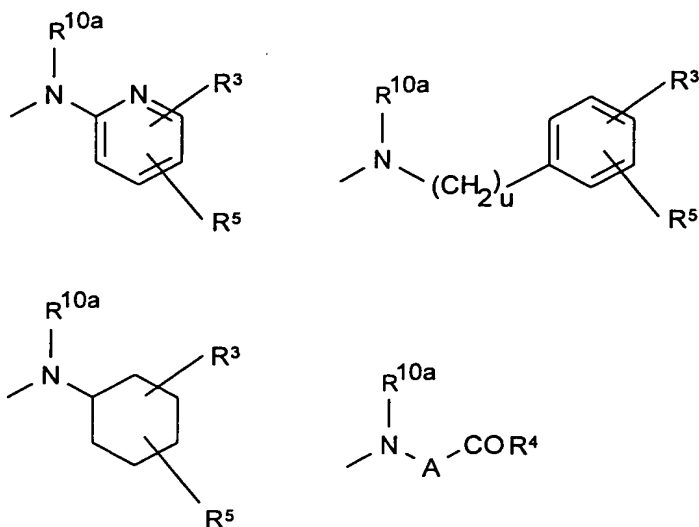
20 Y is >N-CH₂-, >CH-CH₂- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -S-CH₂-, -CH₂-S-, -N(R⁸)-, -(C=O)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and

p and q are 0; and

25 r is 1, 2 or 3; and

Z is selected from



wherein u is 0 or 1;

R³ is -(CH₂)_mOH or -(CH₂)_sCOR⁴ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

5 R⁴ is -OH, -NH₂, -NHOH or C₁₋₆-alkoxy; and

R⁵ is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

R^{10a} is hydrogen or C₁₋₆-alkyl; and

A is C₁₋₆-alkylene, C₂₋₆-alkenylene or C₂₋₆-alkynylene; or

a pharmaceutically acceptable salt thereof.

10

12. The use according to anyone of the claims 1- 2 and 11 wherein the compound is selected from the following:

3-(N-Methyl-N-(3-(10,11-dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)propionic
15 acid;

4-(N-Methyl-N-(3-(10,11-dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)butyric
acid;

20 3-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)propionic acid;

2-(N(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methyl-amino)succinic acid;

2-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

2-(N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)nicotinic acid;

5 2-((N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)methyl)benzoic acid;

2-((N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)-1-cyclohexanecarboxylic acid;

10

2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propylamino)pyridin-3-ol;

3-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

15 2-((3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)benzoic acid;

2-(N-(3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

20 5-Bromo-2-(N-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)benzoic acid,

or a pharmaceutically acceptable salt thereof.

• 13. The use according to anyone of the claims 1-2 wherein in formula Ia
25 R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy;

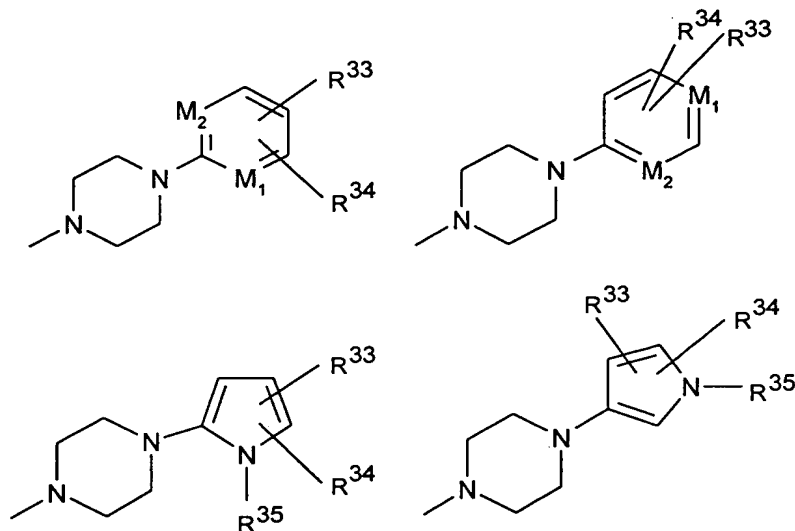
Y is >N-CH₂-, >CH-CH₂-, >C=CH- or >CH-O- wherein only the underscored atom participates in the ring system; and

30 X is ortho-phenylene, -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R⁹)CH₂-, -CH₂CH(R⁹)-, -(C=O)-, -N(R⁸)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and wherein R⁹ is C₁₋₆-alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



5

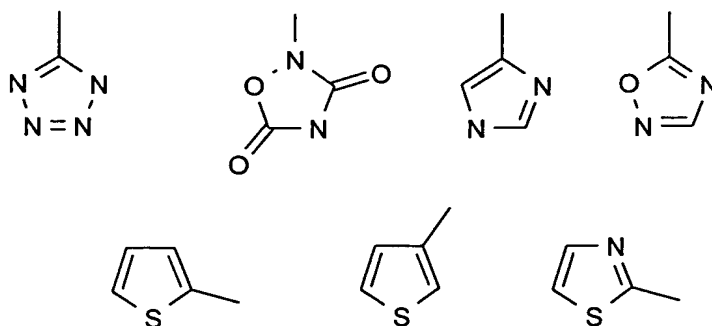
wherein M_1 and M_2 independently are C or N; and

R^{35} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

10 R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6} -alkoxy or NHR^{32} , wherein R^{32} is hydrogen or C_{1-6} -alkyl, and w is 0, 1 or 2; or

R^{34} is selected from



15 or a pharmaceutically acceptable salt thereof.

14. The use according to anyone of the claims 1- 2 and 13 wherein the compound is selected from the following:

2-(4-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(2,10-Dichloro-12H-dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(12H-Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(2-Chloro-12H-dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-piperazin-1-yl)-3-pyridinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(2-pyridyl)piperazine;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propyl)-1-piperazinyl)-3-pyridine-carboxylic acid;

2-(4-(2-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-ethyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

6-(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-2-pyridinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-5-pyridinecarboxylic acid;

2-(4-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

5 1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(2-nitrophenyl)-piperazine;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1-piperazinyl)-benzonitrile;

10 2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1-piperazinyl)-benzoic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(3-trifluoromethyl-2-pyridyl)piperazine;

15

2-(4-(2-(6,11-Dihydro-dibenzo[b,e]thiepin-11-ylidene)ethyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

20 2-(4-(3-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

2-(4-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)ethyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

25 6-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperazin-1-yl)-2-pyridinecarboxylic acid;

2-(4-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

30

6-(4-(3-(Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-piperazin-1-yl)-pyridine-2-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

15. The use according to anyone of the claims 1-2 wherein in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or

5 C_{1-6} -alkoxy; and

Y is $>\underline{N}$ -, $>\underline{CH}$ -, $>\underline{N}-(C=O)$ - or $>\underline{C}=C(R^8)$ -, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6} -alkyl; and

X is ortho-phenylene, -O-, -S-, $-C(R^7R^8)$ -, $-CH_2CH_2$ -, $-CH=CH-CH_2$ -, $-CH_2-CH=CH$ -, $-CH_2-$

$(C=O)$ -, $-(C=O)-CH_2$ -, $-CH_2CH_2CH_2$ -, $-CH=CH$ -, $-N(R^8)-(C=O)$ -, $-(C=O)-N(R^8)$ -, $-O-CH_2$ -, $-CH_2-$

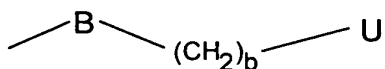
10 O-, $-OCH_2O$ -, $-CH_2OCH_2$ -, $-S-CH_2$ -, $-CH_2-S$ -, $-(CH_2)N(R^8)$ -, $-N(R^8)(CH_2)$ -, $-N(CH_3)SO_2$ -, $-$

$SO_2N(CH_3)$ -, $-CH(R^9)CH_2$ -, $-CH_2CH(R^9)$ -, $-(C=O)$ -, $-N(R^8)$ - or $-(S=O)$ - wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl;

and p and q are 0; and

r is 0, 1, 2, 3 or 4; and

15 Z is



wherein b is 0, 1, 2, 3 or 4; and

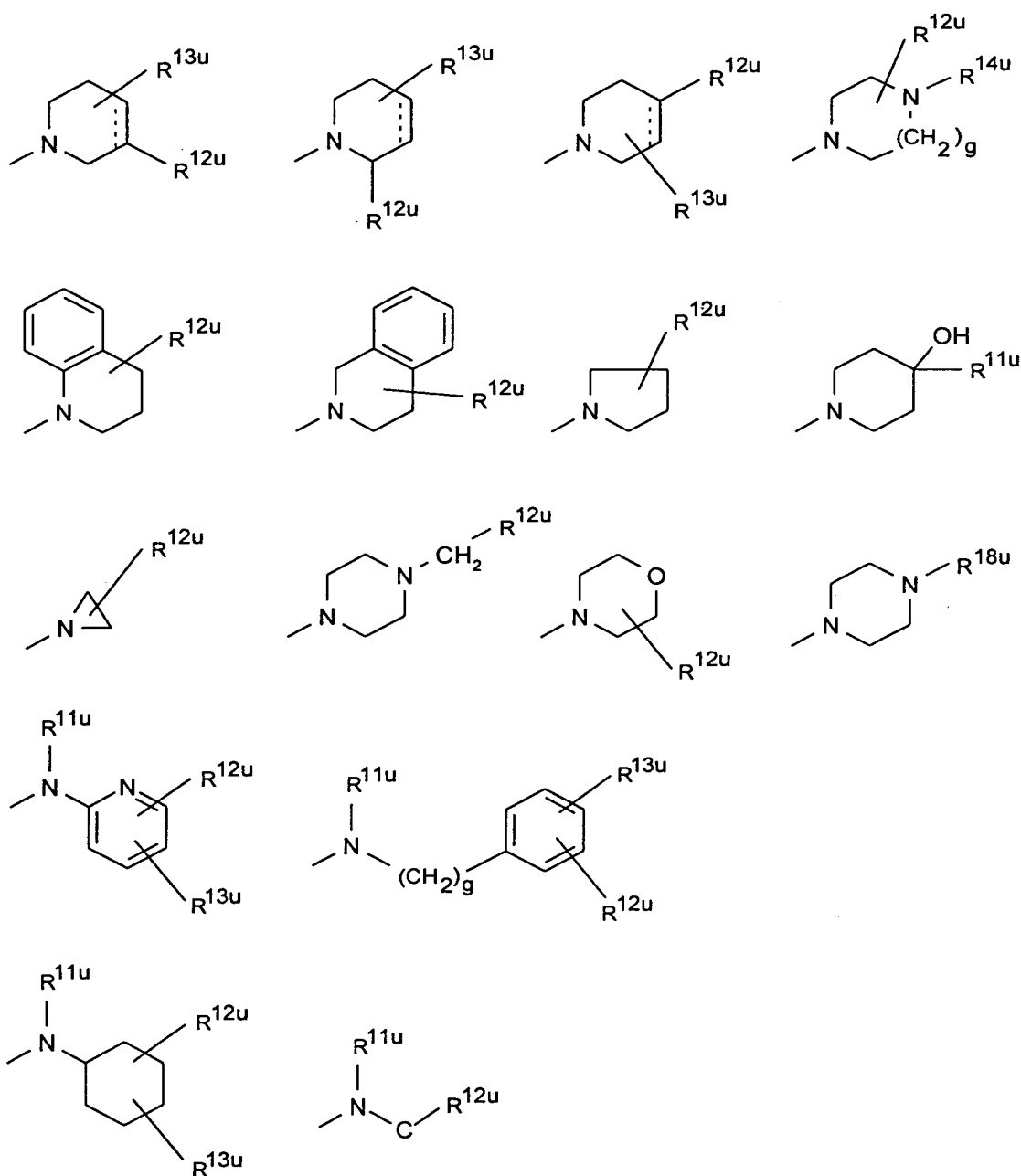
B is $-CH=CR^{49}$ -, $-CR^{49}=CH$ -, $-C\equiv C$ -, $-(C=O)$ -, $-(C=CH_2)$ -, $-(CR^{49}R^{40})$ -, $-CH(OR^{41})$ -, $-$

$CH(NHR^{41})$ -, phenylene, C_{3-7} -cycloalkylene or the completion of a bond, wherein R^{49} and R^{40}

20 independently are hydrogen, C_{1-6} -unbranched alkyl, C_{3-6} -branched alkyl or C_{3-7} -cycloalkyl and

wherein R^{41} is hydrogen or C_{1-6} -alkyl; and

U is selected from



wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

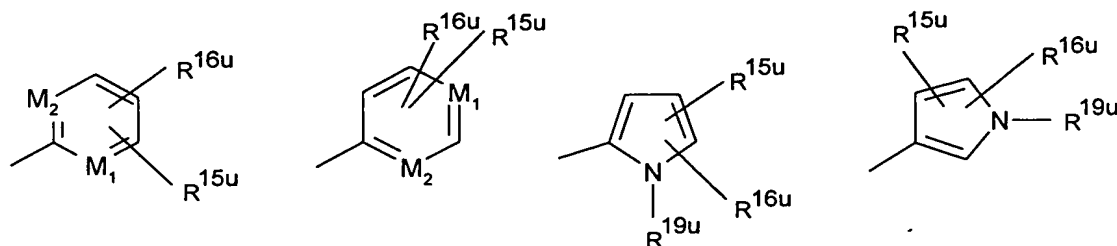
- 5 R^{12u} is -(CH₂)_hOH or -(CH₂)_jCOR^{17u} wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is -OH, -NHR^{20u} or C₁₋₆-alkoxy wherein R^{20u} is hydrogen or C₁₋₆-alkyl; and R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

R^{14u} is hydrogen or C_{1-6} -alkyl; and

C is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; and

... is optionally a single bond or a double bond; and

R^{18u} is selected from



5

wherein M_1 and M_2 independently are C or N; and

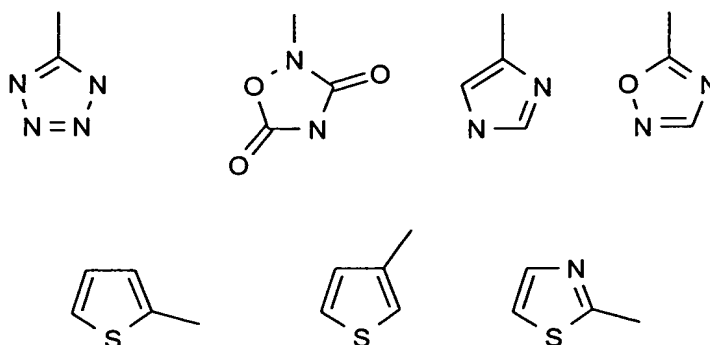
R^{19u} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or -

10 $(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



or a pharmaceutically acceptable salt thereof.

15

16. The use according to anyone of the claims 1- 2 and 15 wherein the compound is selected from the following:

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-

20 piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-4-piperidinecarboxylic acid;

5 1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(2R)-piperidinecarboxylic acid;

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2Z)-butenyl)-(3R)-piperidinecarboxylic acid;

10 1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propionyl)-(3R)-piperidine-carboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-ethyl)-(3R)-piperidine-carboxylic acid;

15 1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2E)-butenyl)-(3R)-piperidinecarboxylic acid;

20 1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-methyl-3-oxopropyl)-(3R)-piperidinecarboxylic acid;

25 1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-butyryl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

30 1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxy-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-dibenzo[b,f]azepin-5-ylmethyl)-1-pentyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Trifluoromethyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-1-piperazinyl)-nicotinic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-cyclopropylmethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-cyclopentylmethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-ethyl)-(3R)-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-3-oxopropyl)-3-piperidinecarboxylic acid;

5 (R)-1-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-benzyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-butyn-1-yl)-3-piperidinecarboxylic acid

10 (R)-1-((2R)-Methyl-3-(3-methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methylpropyl)-3-piperidinecarboxylic acid;

15 (R)-1-(2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidine-carboxylic acid;

20 (R)-1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-3-pyrrolidinylacetic acid;

25 2-(1-(3-(10,11-Dihydrodibenzo[b,f]azepin-5-yl)-(2R)-methylpropyl)-4-piperazinyl)-nicotinic acid;

30 (R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)methyl)-1-pentyl)-3-piperidinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxypropyl)piperazin-1-yl)nicotinic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-methyl-3-oxo-propyl)-3-piperidinecarboxylic acid;

5 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionyl)-4-piperidinecarboxylic acid;

10 (R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylcarbonyl)-1-benzyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-benzyl)-3-piperidinecarboxylic acid;

15 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-3-oxo-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methylpropyl)-4-piperidinecarboxylic acid;

20

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxy-propyl)-4-piperidinecarboxylic acid;

25 (R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxypropyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-propoxypropyl)-4-piperidinecarboxylic acid;

30 (R)-1-(2-(N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-N-methylamino)ethyl)-3-piperidinecarboxylic acid,

or a pharmaceutically acceptable salt thereof.

17. The use according to anyone of the claims 1-2 wherein in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy or methylthio, $-NR^7R^8$ or $-SO_2NR^7R^8$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and

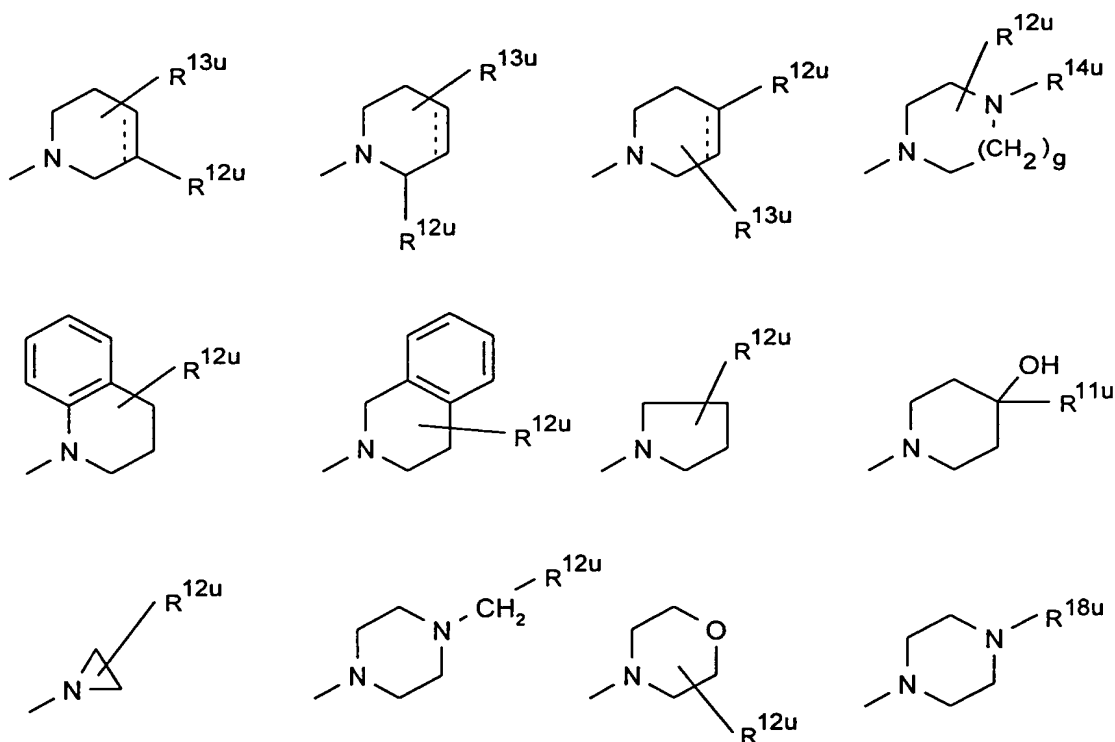
Y is $>\underline{CH}-O-$ or $>\underline{CH}-S(O)_y$ wherein y is 0, 1 or 2, or $-N(R^8)-$ wherein R^8 is hydrogen or C_{1-6} -alkyl; and

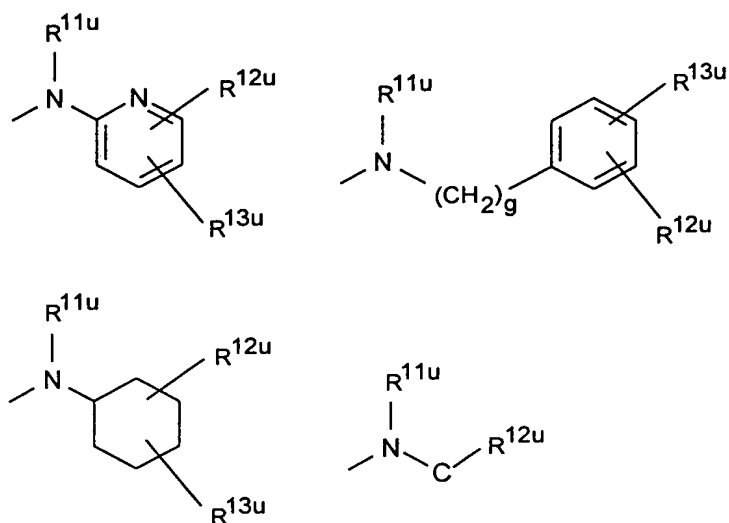
X is completion of an optional bond, ortho-phenylene, $-O-$, $-S-$, $-C(R^7R^8)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-CH_2OCH_2-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^9)CH_2-$, $-CH_2CH(R^9)-$, $-(C=O)-$, $-N(R^8)-$ or $-(S=O)-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

p and q independently are 0 or 1; and

r is 1, 2, 3 or 4; and

Z is selected from





wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen,

5 trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and

wherein R^{17u} is $-OH$, $-NHR^{20u}$ or C_{1-6} -alkoxy wherein R^{20u} is hydrogen or C_{1-6} -alkyl; and

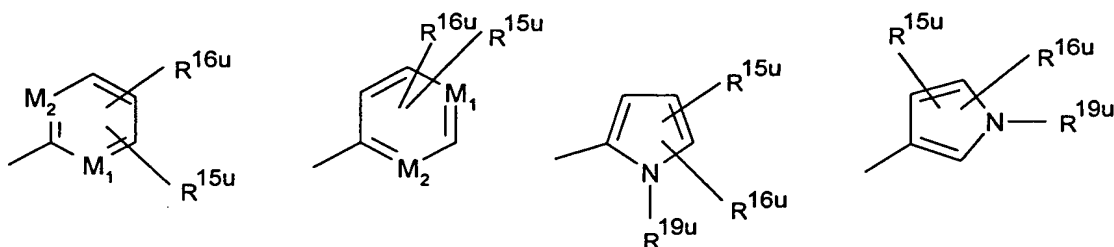
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

R^{14u} is hydrogen or C_{1-6} -alkyl; and

10 C is C_{1-6} -alkylene, C_{2-6} -alkenylene or C_{2-6} -alkynylene; and

... is optionally a single bond or a double bond; and

R^{18u} is selected from



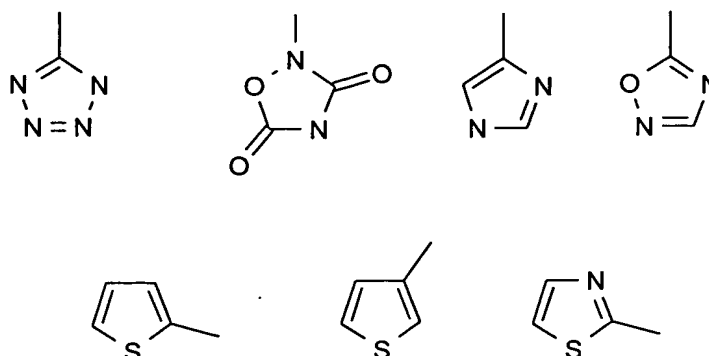
wherein M_1 and M_2 independently are C or N; and

15 R^{19u} is hydrogen, C_{1-6} -alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



or a pharmaceutically acceptable salt thereof.

5

18. The use according to anyone of the claims 1- 2 and 17 wherein the compound is selected from the following:

10 1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

15 1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

20

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

25

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

5

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

10

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid,

15

or a pharmaceutically acceptable salt thereof.

19. The use according to anyone of the claims 1-2 wherein in formula Ia

20

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

Y is $>\underline{N}$ -CH₂-, $>\underline{C}$ H-CH₂- or $>\underline{C}$ =CH- wherein only the underscored atom participates in the ring system; and

25

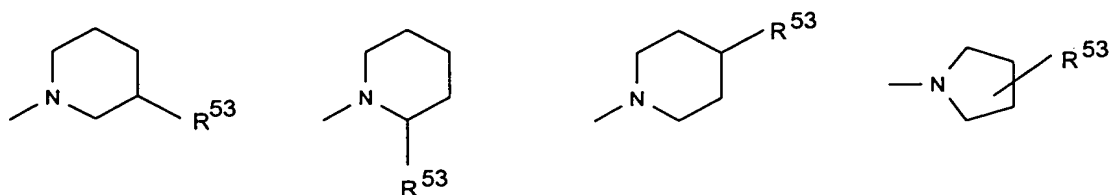
X is ortho-phenylene, -O-, -S-, -C(R^7 R^8)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R^8)-, -N(R^8)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R^9)CH₂-, -CH₂CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

30

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



wherein R^{53} is $-(CH_2)_{pp}COOH$ wherein pp is 2, 3, 4, 5 or 6; or a pharmaceutically acceptable salt thereof.

- 5 20. The use according to anyone of the claims 1- 2 and 19 wherein the compound is selected from the following:

3-(1-(3-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-3-yl)propionic acid;

10

3-(1-(3-(10,11-Dihydrodibenzo[b,f]azepin-5-yl)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(2-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)ethyl)piperidin-4-yl)propionic acid;

15

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)piperidin-4-yl)propionic acid;

20

3-(1-(3-(Thioxanthen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

25

3-(1-(3-(Xanthen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

30

4-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)-butyric acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-2-yl)-propionic acid;

3-(1-(3-(1-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

5 3-(1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Trifluoromethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-piperidin-4-yl)propionic acid;

10

3-(1-(3-(2-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

15 3-(1-(3-(2-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-piperidin-4-yl)propionic acid;

20 3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

25

3-(1-(3-(2-Fluoro-6,11-dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)-propionic acid;

4-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)butyric acid;

30 3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-2-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)-propionic acid;

4-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)-butyric acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(10H-Anthracen-9-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(10H-Anthracen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

5-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(Thioxanthen-9-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid,

or a pharmaceutically acceptable salt thereof.

21. The use according to anyone of the claims 1-2 wherein in formula Ia

R¹, R^{1a}, R² and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

Y is >N-CH₂-, >CH-CH₂-, >C=CH- or >CH-O- wherein only the underscored atom participates in the ring system; and

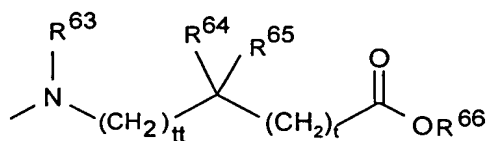
X is ortho-phenylene, -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-

O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R⁹)CH₂-, -CH₂CH(R⁹)-, -(C=O)-, -N(R⁸)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and wherein R⁹ is C₁₋₆-alkyl or phenyl; and

p and q are 0; and

5 r is 1, 2 or 3; and

Z is



wherein tt and t independently are 0, 1 or 2; and

10 R⁶³ is H, C₁₋₆-alkyl or optionally substituted benzyl;

R⁶⁴ and R⁶⁵ independently are H, C₁₋₈-alkyl, C₃₋₇-cycloalkyl, phenyl, thienyl, benzyl, or R⁶⁴ and R⁶⁵ together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring; and

R⁶⁶ is H or C₁₋₆-alkyl; or

15 a pharmaceutically acceptable salt thereof.

22. The use according to anyone of the claims 1- 2 and 21 wherein the compound is selected from the following:

20 1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

25

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

30

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

10 (R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

15 (R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

20 (R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid,

or a pharmaceutically acceptable salt thereof.

23. The use according to anyone of the claims 1-2 wherein in formula Ia R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

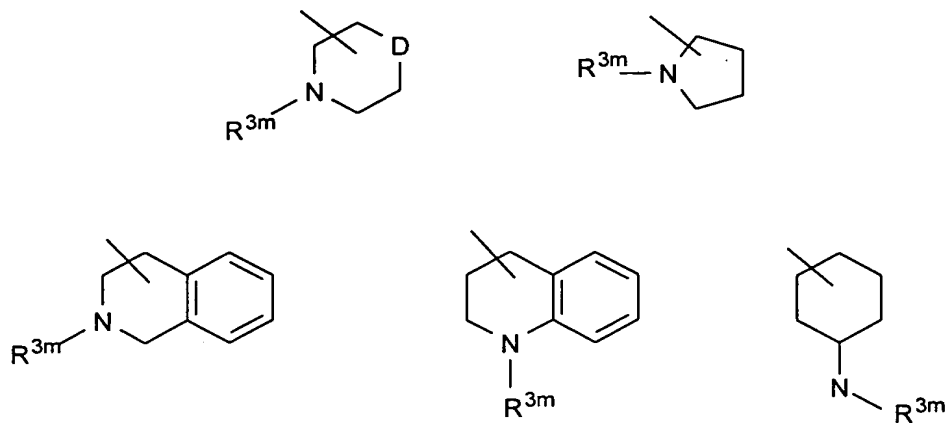
Y is $\text{>N-CH}_2\text{-}$, $\text{>CH-CH}_2\text{-}$ or >C=CH- wherein only the underscored atom participates in the ring system; and

30 X is ortho-phenylene, -O-, -S-, $-\text{C}(\text{R}^7\text{R}^8)\text{-}$, $-\text{CH}_2\text{CH}_2\text{-}$, $-\text{CH=CH-CH}_2\text{-}$, $-\text{CH}_2\text{-CH=CH-}$, $-\text{CH}_2\text{-(C=O)-}$, $-(\text{C=O})\text{-CH}_2\text{-}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-}$, $-\text{CH=CH-}$, $-\text{N}(\text{R}^8)\text{-(C=O)-}$, $-(\text{C=O})\text{-N}(\text{R}^8)\text{-}$, $-\text{O-CH}_2\text{-}$, $-\text{CH}_2\text{-O-}$, $-\text{OCH}_2\text{O-}$, $-\text{S-CH}_2\text{-}$, $-\text{CH}_2\text{-S-}$, $-(\text{CH}_2)\text{N}(\text{R}^8)\text{-}$, $-\text{N}(\text{R}^8)(\text{CH}_2)\text{-}$, $-\text{N}(\text{CH}_3)\text{SO}_2\text{-}$, $-\text{SO}_2\text{N}(\text{CH}_3)\text{-}$, $-\text{CH}(\text{R}^9)\text{CH}_2\text{-}$, $-\text{CH}_2\text{CH}(\text{R}^9)\text{-}$, $-(\text{C=O})\text{-}$, $-\text{N}(\text{R}^8)\text{-}$ or $-(\text{S=O})\text{-}$ wherein R^7 and R^8 independently are hydrogen or C_{1-6} -alkyl; and wherein R^9 is C_{1-6} -alkyl or phenyl; and

p and q are 0; and

r is 0, 1 or 2; and

Z is selected from



- 5 wherein D is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$ or $-\text{N}(\text{R}^7)-$ wherein R^7 is H or C_{1-6} -alkyl; and R^{3m} is $-(\text{CH}_2)_{mm}\text{OH}$ or $-(\text{CH}_2)_{mp}\text{COR}^4$ wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH_2 , NHOH or C_{1-6} -alkoxy; or a pharmaceutically acceptable salt thereof.

- 10 24. The use according to anyone of the claims 1- 2 and 23 wherein the compound is selected from the following:

3-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-pyrrolidin-1-yl)-propionic acid;

- 15 (2-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-morpholin-4-yl)-acetic acid;

(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-ylmethyl)-1-piperidyl)acetic acid,

or a pharmaceutically acceptable salt thereof.

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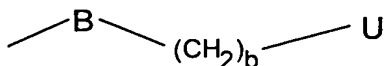
25. The use according to anyone of the claims 1-2 wherein in formula Ia

R^1 , R^{1a} , R^2 and R^{2a} independently are hydrogen, halogen, cyano, trifluoromethyl, methylthio, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

Y is $>\underline{\text{N}}-$, $>\underline{\text{C}}\text{H}-$, $>\underline{\text{N}}-(\text{C}=\text{O})-$ or $>\underline{\text{C}}=\text{C}(\text{R}^8)-$, wherein only the underscored atom participates in

- 25 the ring system and R^8 is hydrogen or C_{1-6} -alkyl; and

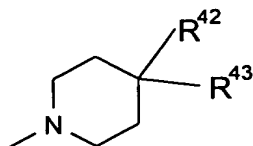
X is ortho-phenylene, -O-, -S-, -C(R⁷R⁸)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R⁸)-(C=O)-, -(C=O)-N(R⁸)-, -O-CH₂-, -CH₂-O-, -OCH₂O-, -CH₂OCH₂-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R⁸)-, -N(R⁸)(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R⁹)CH₂-, -CH₂CH(R⁹)-, -(C=O)-, -N(R⁸)- or -(S=O)- wherein R⁷ and R⁸ independently are hydrogen or C₁₋₆-alkyl; and wherein R⁹ is C₁₋₆-alkyl or phenyl; and p and q are 0; and r is 0, 1, 2, 3 or 4; and Z is



wherein b is 0, 1, 2, 3 or 4; and

B is -CH=CR⁴⁹-, -CR⁴⁹=CH-, -C≡C-, -(C=O)-, -(C=CH₂)-, -(CR⁴⁹R⁴⁰)-, -CH(OR⁴¹)-, -CH(NHR⁴¹)-, phenylene, C₃₋₇-cycloalkylene or the completion of a bond, wherein R⁴⁹ and R⁴⁰ independently are hydrogen, C₁₋₆-unbranched alkyl, C₃₋₆-branched alkyl or C₃₋₇-cycloalkyl and wherein R⁴¹ is hydrogen or C₁₋₆-alkyl; and

U is



wherein R⁴² is hydrogen, -(CH₂)_cOH or -(CH₂)_cCOR⁴⁷ wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R⁴⁷ is -OH, -NHR⁴⁴ or C₁₋₆-alkoxy wherein R⁴⁴ is hydrogen or C₁₋₆-alkyl; and

R⁴³ is cyano, -NR⁴⁵R⁴⁶, -NR⁴⁵-V or -(CHR⁴⁸)_e-V wherein R⁴⁵ and R⁴⁶ independently are hydrogen or C₁₋₆-alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R⁴⁸ is hydrogen, halogen, cyano, trifluoromethyl, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, -NR⁴⁵R⁴⁶ or -COOH, and wherein V is C₃₋₈-cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C₁₋₆-alkyl or C₁₋₆-alkoxy; or a pharmaceutically acceptable salt thereof.

26. The use according to anyone of the claims 1- 2 and 25 wherein the compound is selected from the following:

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-phenyl-4-piperidinecarboxylic acid;

4-(4-Chlorophenyl)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

4-(4-Methylphenyl)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-anilino-4-piperidinecarboxamide;

2-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidyl)-2-phenylacetonitrile;

2-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidiny)-2-phenylacetic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-cyano-4 piperidine-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

27. The use according to anyone of the claims 1-2 wherein in formula Ib

R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy; and

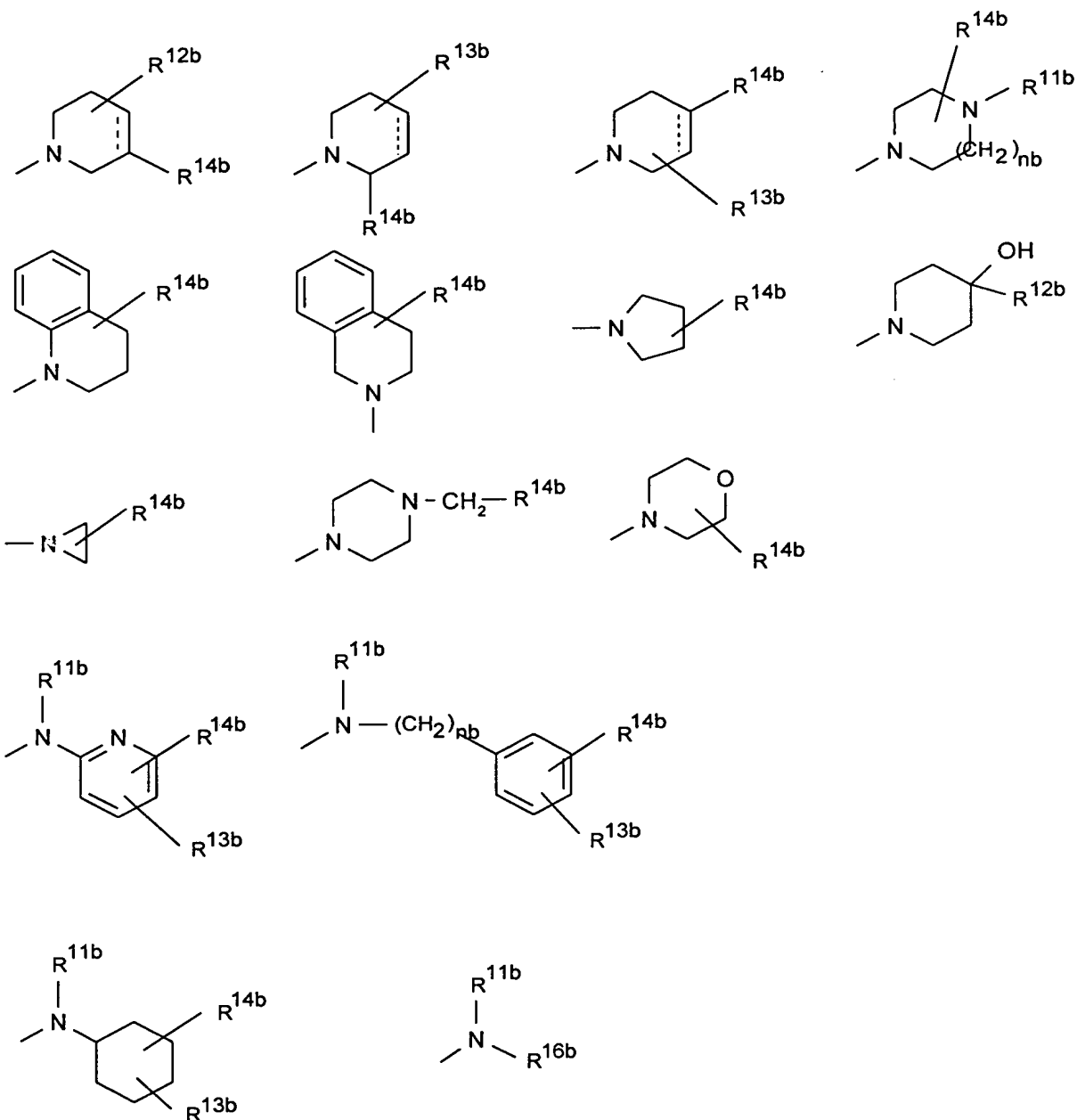
R^{3b} is hydrogen or C₁₋₃-alkyl; and

A_b is C₁₋₃-alkylene; and

Y_b is >CH-CH₂-, >C=CH-, >CH-O-, >C=N-, >N-CH₂- wherein only the underscored atom

participates in the ring system; and

Z_b is selected from



- 5 wherein nb is 1 or 2; and
 R^{11b} is hydrogen or C_{1-6} -alkyl; and
 R^{12b} is hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and
 R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and
 10 R^{14b} is $-(CH_2)_{mb}OH$ or $-(CH_2)_{tb}COR^{15b}$ wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and wherein R^{15b} is $-OH$, NH_2 , $-NHOH$ or C_{1-6} -alkoxy; and

R^{16b} is C₁₋₆-alkyl or -B_b-COR^{15b}, wherein B_b is C₁₋₆-alkylene, C₂₋₆-alkenylene or C₂₋₆-alkynylene and R^{15b} is the same as above; and

... is optionally a single bond or a double bond; or
a pharmaceutically acceptable salt thereof.

28. The use according to anyone of the claims 1- 2 and 27 wherein the compound is selected from the following:

2-Chloro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(2-dimethylamino)ethoxy-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(3-dimethylamino)propyl-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(3-dimethylamino-1-methyl)ethoxy-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(2-dimethylaminopropylidene)-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-dimethylamino-1-methylpropylidene)-12H-dibenzo-[d,g][1,3]dioxocine;

2-Fluoro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

2-Methyl-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

2-Chloro-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)propyl)-3-piperidinecarboxylic acid ethyl ester;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)propyl)-3-piperidinecarboxylic acid,

or a pharmaceutically acceptable salt thereof.

29. The use according to anyone of the claims 1-2 wherein in formula Ic

R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and

X_c is ortho-phenylene, -O-, -S-, -C($R^{6c}R^{7c}$)-, -CH₂CH₂-, -CH=CH-CH₂-, -CH₂-CH=CH-, -CH₂-(C=O)-, -(C=O)-CH₂-, -CH₂CH₂CH₂-, -CH=CH-, -N(R^{8c})-(C=O)-, -(C=O)-N(R^{8c})-, -O-CH₂-, -CH₂-

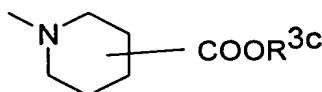
O-, -OCH₂O-, -S-CH₂-, -CH₂-S-, -(CH₂)N(R^{8c})-, -N(R^{8c})(CH₂)-, -N(CH₃)SO₂-, -SO₂N(CH₃)-, -CH(R^{10c})CH₂-, -CH₂CH(R^{10c})-, -(C=O)-, -N(R^{9c})- or -(S=O)- wherein R^{6c} , R^{7c} , R^{8c} and R^{9c} independently are hydrogen or C_{1-6} -alkyl, and wherein R^{10c} is C_{1-6} -alkyl or phenyl; and

Y_c is C or N; and

... is optionally a single bond or a double bond, and ... is a single bond when Y_c is N; and

mc is 1, 2, 3, 4, 5 or 6; and

Z_c is -COOR^{3c} or



wherein R^{3c} is H or C_{1-6} -alkyl; or

a pharmaceutically acceptable salt thereof.

30.

The use according to anyone of the claims 1- 2 and 29 wherein the compound is selected from the following:

1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidine-carboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidine-carboxylic acid;

5 1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

10 1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

15 (R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

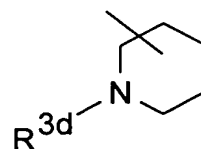
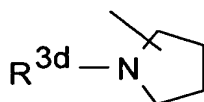
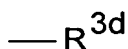
(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

20 (R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid,

25 or a pharmaceutically acceptable salt thereof.

31. The use according to anyone of the claims 1-2 wherein in formula Id
 R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6} -alkyl or C_{1-6} -alkoxy; and
 30 X_d is -O-, -S- or -S(=O)-; and
 n_d is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ; and
 Z_d is selected from



wherein R^{3d} is $-(CH_2)_{md}OH$ or $-(CH_2)_{pd}COR^{4d}$ wherein md and pd independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2 , $NHOH$ or C_{1-6} -alkoxy; or a pharmaceutically acceptable salt thereof.

5

32. The use according to anyone of the claims 1- 2 and 31 wherein the compound is selected from the following:

4-(1,3,4,14b-Tetrahydro-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]oxazepin-2-yl)-butanoic acid;

10

4-(1,3,4,14b-Tetrahydro-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]thiazepin-2-yl)-butanoic acid,

or a pharmaceutically acceptable salt thereof.

15

33. The use according to any of the claims 1-32 wherein the pharmaceutical composition is in a form suitable for oral administration.

34. A method of treating an indication related to angiogenesis comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1-32.

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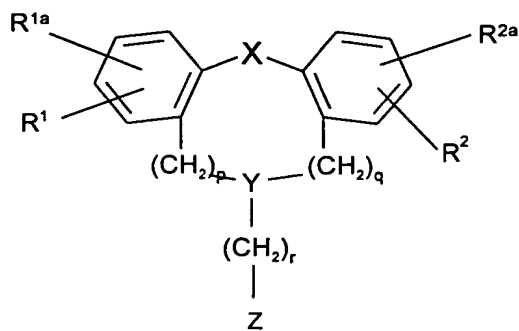
35. A method according to any of the claims 34 wherein angiogenesis is related to cancer.

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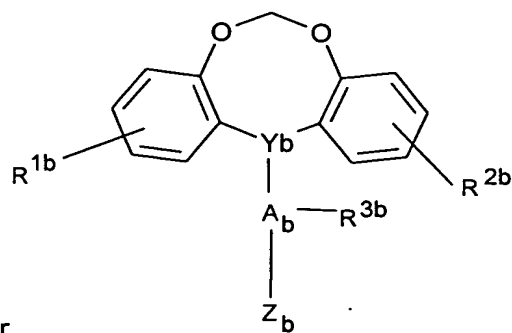
36. Any novel feature or combination of features described herein.

ABSTRACT

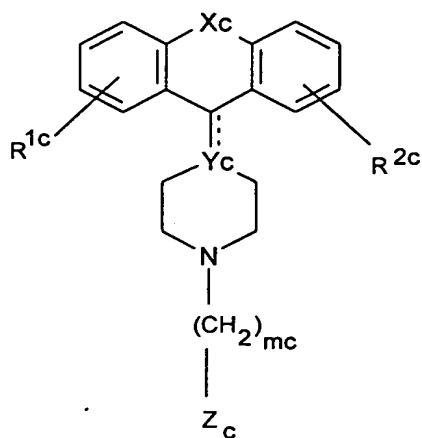
The present invention relates to the use of compounds having the general formulas



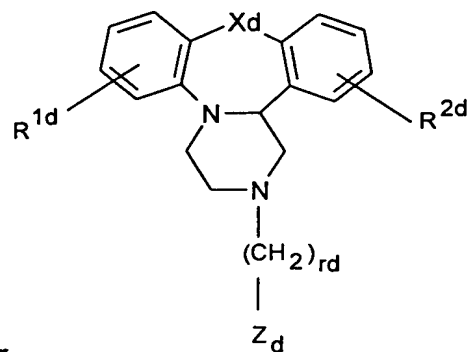
(Ia)



(Ib)



(Ic)



(Id)

wherein R¹, R^{1a}, R², R^{2a}, X, Y, Z, p, q, r, R^{1b}, R^{2b}, R^{3b}, Y_b, A_b, Z_b, R^{1c}, R^{2c}, X_c, Y_c, Z_c, mc, R^{1d}, R^{2d}, X_d, Z_d and rd are as defined in the detailed part of the present description, or salts thereof, for the treatment of indications related to angiogenesis.